An examination of systems of access to important high cost medicines: a critical analysis of the nationally subsidised scheme of access to tumour necrosis factor inhibitors in Australia

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AN EXAMINATION OF SYSTEMS OF ACCESS TO IMPORTANT HIGH COST MEDICINES:

A CRITICAL ANALYSIS OF THE NATIONALLY SUBSIDISED SCHEME OF ACCESS TO TUMOUR NECROSIS FACTOR INHIBITORS IN AUSTRALIA

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STATEMENT OF ORIGINALITY

The research presented in this thesis was carried out under the supervision of **Professor Richard O. Day** (Professor of Clinical Pharmacology, School of Medical Sciences, the University of New South Wales, and Director, Department of Clinical Pharmacology & Toxicology, St Vincent's Hospital Sydney), and **Associate Professor Kenneth M. Williams** (Associate Professor, School of Medical Sciences, the University of New South Wales, and Deputy Director, Department of Clinical Pharmacology & Toxicology, St Vincent's Hospital Sydney).

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Christine Y Lu

30 November 2006

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ABSTRACT

Background: Access to "high-cost medicines" under Australia's Pharmaceutical Benefits Scheme (PBS) is characterised by strict eligibility criteria. The PBS access scheme for the anti-rheumatic biologicals (etanercept, infliximab, and adalimumab) was examined for concordance with Australia's National Medicines Policy.

Methods: Semi-structured interviews with a range of stakeholders were conducted. National, aggregated prescription and expenditure data from Medicare Australia and dispensing data from the Drug Utilisation Sub-Committee were analysed. Access to biologicals was also examined from an ethical perspective.

Results: Interviewees agreed that controlled access to high-cost medicines was broadly equitable and practical but specific concerns included: timeliness of access; bureaucracy of the process; contentious cases of individual patients being denied access; insufficient patient information; the quantum of resources required to administer the access scheme; inadequate stakeholder consultation. The access requirement of a history of failure of conventional anti-rheumatic drugs was supported. Recommendations included proactive review of the access criteria and outcomes; greater transparency and formal stakeholder involvement to increase public confidence in the definition of "target patient population"; and a formal appeal mechanism to increase the fairness and accountability of the PBS. Establishment of an appeal mechanism is supported by "accountability for reasonableness" framework grounded in procedural justice.

Data needed to examine the health outcomes associated with the use of biologicals on a national level was not easily available. This shortcoming is discordant with National Medicines Policy. Utilisation of biologicals over the first two years of PBS-subsidy was conservative but with considerable variability across States and Territories (an 8-fold difference between the jurisdictions), usage roughly correlating with access to rheumatologists. Introduction of PBS-subsidised biologicals did not alter the trends in utilisation of non-biological anti-rheumatic drugs.

Conclusions: This research suggests that policy-makers focus upon: explicitly considering ethical principles and formally involving stakeholders when developing policies on access to high-cost medicines; improving communication and providing information based on increased transparency; and establishing formal mechanisms for review of and appeals against PBS decisions. The comprehensive evaluation of medicine use and outcomes post-subsidy is critical for the future of the PBS. The National Medicines Policy has proved a useful framework for evaluating this access scheme.

COMMUNICATIONS ARISING FROM THIS THESIS

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PEER REVIEWED PUBLICATIONS

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2007   Day RO, **Lu CY**, Pearce G, Grainger D. Pharmaceutical Benefits Scheme: rapid change and impetus towards achieving Quality Use of Medicines. J Pharm Prac Res 2007; 37:4-5

2007   Lu CY, Williams K, Day R. The funding and use of high-cost medicines in Australia: the example of anti-rheumatic biological medicines. Aus NZ Health Policy 2007: 4:2 URL: http://www.anzhealthpolicy.com

2006   Kaye K, **Lu CY**, Day R. Can we deny patients expensive drugs? Aus Presc 2006; 29:146-148

2006   Lu CY, Williams K, Day R. Accessing health outcome data on high-cost medicines in Australia. Med J Aust 2006; 184: 411-413

2006   Lu CY. Health outcomes conferences. J Pharm Prac Res 2006; 36:77-78 (Letter)

2006   Lu CY, Williams K, Day R. Access to tumour necrosis factor inhibitors for Rheumatoid Arthritis treatment under the Australian Pharmaceutical Benefits Scheme. Are we on target? Intern Med J 2006; 36:19-27

2005   Lu CY, Ritchie J, Williams K, Day R. Recent developments in targeting access to high cost medicines in Australia. Aus NZ Health Policy 2005; 2:28 URL: http://www.anzhealthpolicy.com

2005   Hall W, Ward R, Liauw W, Brien J, **Lu CY**. Tailoring access to high cost, genetically targeted drugs. Med J Aust 2005; 182:607-608 (Editorial)

2004   Lu CY, Williams K, March L, Bertouch J, Day R. Subsidised access to TNF-alpha inhibitors: is the rationale for exclusion of rheumatoid factor negative patients defensible? Med J Aust 2004; 181:457-458 (Letter)

2004   Lu CY, March L, Sansom L, Bertouch J, Williams K, Day R. Access to high cost drugs in Australia *Risk sharing scheme may set a new paradigm*. BMJ 2004; 329:415-416 (Editorial)

PUBLISHED ABSTRACTS

2006   Lu CY, Williams K, Day R. Utilisation of anti-rheumatic drugs in Australia: Impact of introducing high-cost biologics under the Pharmaceutical Benefits Scheme. Pharmacoepidemiol Drug Saf 2006; 15: S213

2006   Lu CY, Williams K, Day R. Access to high-cost medicines for the treatment of rheumatoid arthritis under Australia's Pharmaceutical Benefits Scheme. Pharmacoepidemiol Drug Saf 2006; 15: S213

2006   Lu CY, Williams K, Day R. Community use of anti-rheumatic drugs: impact of introducing biologics under the Pharmaceutical Benefits Scheme. & Access to biologics for the treatment of rheumatoid arthritis under the Pharmaceutical Benefits Scheme: Two years utilisation. Intern Med J 2006; 36 (s2): A66

2006   Lu CY, Ritchie J, Williams K, Day R. Targeted access to high-cost medicines in Australia: Stakeholders' perceptions. Inter Med J 2006; 36 (s2): A81

2005   Lu CY, Ritchie J, Williams K, Day R. Targeting access to high-cost medicines in Australia: Early analysis from a qualitative study. Value in Health 2005; 8:A28.

2005   Lu CY, Williams K, Day R. Evaluation of access to high-cost medicines in Australia using national claims data. Value in Health 2005; 8:A28

2005   Lu CY, Williams K, Day R. Access to tumour necrosis factor inhibitors under the Pharmaceutical Benefits Scheme: First year utilisation. Intern Med J 2005; 35:A99

2005   Lu CY, Ritchie J, Williams K, Day R. Restricted access to tumour necrosis factor inhibitors in Australia: preliminary findings from a qualitative study. Intern Med J 2005; 35:A99

2004   Lu CY, Williams K, Day R. Access to high cost drugs – The example of etanercept. 8th World Congress Clinical Pharmacology & Therapeutics, Brisbane, Australia, August 2004. Clin Exp Pharmacol Physiol 2004; 31(Suppl 1):A83 PO-127

2004   Lu CY, Williams K, March L, Bertouch J, Day R. Lack of evidence for an association between rheumatoid factor status and clinical response in patients with rheumatoid arthritis treated with TNF-alpha inhibitors. Intern Med J 2004; 34:A104

SCIENTIFIC PRESENTATIONS – International Conferences

2005   Lu CY, Ritchie J, Williams K, Day R. Targeting access to high-cost medicines in Australia: Early analysis from a qualitative study. International Society for Pharmacoeconomics & Outcomes Research 8th Annual European Congress, Florence, Italy

2005   Lu CY, Williams K, Day R. Evaluation of access to high-cost medicines in Australia using national claims data. International Society for Pharmacoeconomics & Outcomes Research 8th Annual European Congress, Florence, Italy

2005   Lu CY, Williams K, Day R. Access to high cost medicines in Australia: Evaluation of patient outcomes using national administrative data. 6th International Conference on Health Policy Research, Boston, United States

2004   Lu CY, Williams K, Day R. Access to high cost drugs – The example of etanercept. 8th World Congress Clinical Pharmacology & Therapeutics, Brisbane, Australia

SCIENTIFIC PRESENTATIONS – Australasian Conferences

2006   Lu CY, Ritchie J, Williams K, Day R. Access to high-cost medicines in Australia: Views of stakeholders. 4th National Medicines Symposium, Canberra

2006   Lu CY, McNeill P, Williams K, Day R. Controlled access to high cost medicines: Ethical issues. 4th National Medicines Symposium, Canberra

2006   Lu CY, Ritchie J, Williams K, Day R. Targeted access to high-cost medicines in Australia: Stakeholders' perceptions. 48th Australian Rheumatology Association Annual Conference, Perth

2006   Lu CY, Williams K, Day R. Community use of anti-rheumatic drugs: impact of introducing biologics under the Pharmaceutical Benefits Scheme. & Access to biologics for the treatment of rheumatoid arthritis under the Pharmaceutical Benefits Scheme: Two years utilisation. 48th Australian Rheumatology Association Annual Conference, Perth

2005   Lu CY, Williams K, Day R. Utilisation of anti-rheumatic drugs in Australia: impact of introducing biological agents under the Pharmaceutical Benefits Scheme. Australiasian Society of Clinical and Experimental Pharmacologists and Toxicologists joint Annual Scientific Meeting with Australasian Pharmaceutical Science Association, Melbourne

2005   Lu CY, Williams K, Day R. Utilisation of tumour necrosis factor inhibitors for rheumatoid arthritis under the Pharmaceutical Benefits Scheme. 15th St Vincent's & Mater Health Sydney Research Symposium, Sydney

2005   Lu CY, Williams K, Day R. Evaluation of access to tumour necrosis factor inhibitors impaired by inadequate access to and content of HIC database. National Health Outcomes Conference, Canberra

2005   Lu CY, Williams K, Day R. Access to tumour necrosis factor inhibitors under the Pharmaceutical Benefits Scheme: First year utilisation. 47th Australian Rheumatology Association Annual Conference, Melbourne

2005   Lu CY, Ritchie J, Williams K, Day R. Restricted access to tumour necrosis factor inhibitors in Australia: preliminary findings from a qualitative study. 47th Australian Rheumatology Association Annual Conference, Melbourne

2004   Lu CY, Williams K, Day R. Safety of tumour necrosis factor-alpha antagonists - The Australian experience. 4th Biennial Society of Hospital Pharmacists of Australia Clinical Conference, Sydney

2004   Lu CY, Williams K, Day R. Access to etanercept via the Pharmaceutical Benefits Scheme. 3rd Australian National Medicines Symposium, Brisbane

2004   Lu CY, Williams K, March L, Bertouch J, Day R. Lack of evidence for an association between rheumatoid factor status and clinical response in patients with rheumatoid arthritis treated with TNF-alpha inhibitors. 46th Australian Rheumatology Association Annual Conference, Cairns

PRESENTATIONS – Others

2006 "*Access to tumour necrosis factor inhibitors for the treatment of rheumatoid arthritis via the Pharmaceutical Benefits Scheme: a qualitative study*" Research Seminar, Department of Clinical Pharmacology, St. Vincent's Hospital Sydney, Australia

2005 "*Access to tumour necrosis factor inhibitors under the Pharmaceutical Benefits Scheme: First year utilisation*" (Poster). Research Day, Faculty of Medicine, University of New South Wales, Sydney, Australia

2005 "*Access to high-cost medicines via the Pharmaceutical Benefits Scheme: a case study of tumour necrosis factor inhibitors for the treatment of rheumatoid arthritis*" Research Seminar, Department of Clinical Pharmacology, St. Vincent's Hospital Sydney, Australia

2004 "*Lack of evidence for an association between rheumatoid factor status and clinical response in patients with rheumatoid arthritis treated with TNF-alpha inhibitors*" (Poster). Research Day, Faculty of Medicine, University of New South Wales, Sydney, Australia

2004 "*Access to tumour necrosis factor inhibitors via the Pharmaceutical Benefits Scheme*". Research Seminar, Department of Clinical Pharmacology, St. Vincent's Hospital Sydney, Australia

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GLOSSARY OF ABBREVIATIONS

A$	Australian Dollars
ABS	Australian Bureau of Statistics
ACR	American College of Rheumatology
ADEC	Australian Drug Evaluation Committee
ADR	Adverse Drug Reaction
ADRAC	Adverse Drug Reactions Advisory Committee
AIHW	Australian Institute of Health and Welfare
ARA	Australian Rheumatology Association
ARAD	Australian Rheumatology Association Database
AUSFTA	Australia-United States Free Trade Agreement
BEACH	Bettering the Evaluation and Care of Health
BSR	British Society for Rheumatology
CRP	C-reactive protein
DAS	Disease Activity Score
DMARD(s)	Disease modifying anti-rheumatic drug(s)
DTC(s)	Drug and Therapeutic Committee(s)
DUSC	Drug Utilisation Sub-Committee of the PBAC
DVA	Department of Veterans' Affairs
EBM	Evidence-based medicine
EMEA	European Agency for the Evaluation of Medicinal Products
ESC	Economic Sub-Committee of the PBAC
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration, United States
GDP	Gross Domestic Product
GP(s)	General practitioner(s)
GPRN	General Practice Research Network
HCM(s)	High cost medicine(s)
MCQ	Hydroxychloroquine
HREC	Human Research and Ethics Committee
LEF	Leflunomide
MBS	Medicare Benefits Scheme
MTX	Methotrexate

NICE	National Institute for Health and Clinical Excellence, United Kingdom
NMP	National Medicines Policy
NPS	National Prescribing Service
OECD	Organisation for Economic Cooperation and Development
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBS	Pharmaceutical Benefits Scheme
PEN	Penicillamine
PES	Pharmaceutical Evaluation Section
QALY	Quality-adjusted life-years
QUM	Quality Use of Medicines
RA	Rheumatoid arthritis
RCT(s)	Randomised controlled trial(s)
RF	Rheumatoid factor
SF-36	Short form questionnaire
SULF	Sulfasalazine
TGA	Therapeutic Goods Administration
TNF	Tumour necrosis factor-alpha
TRIPS	Trade-Related Intellectual Property Rights Agreement
UK	United Kingdom
USA, US	United States of America
US$	American Dollars
WHO	World Health Organisation

PREFACE

This thesis investigates the little researched area of access to high cost medicines via publicly-funded, national drug subsidy programs. Access to "essential" medicines is a critical component of healthcare systems. Drug reimbursement programs of both public and private healthcare systems grapple with the challenges of funding innovative medicines as healthcare resources are finite. The more recent availability of biotechnology-derived pharmaceutical products, which are commonly more expensive, has highlighted this dilemma.

The Australian healthcare system is considered to be amongst the best in the world.(1) One reason for this may be because Australia has a national medicines policy. Within this policy, government-subsidised access to a wide range of prescription medicines is provided by the Pharmaceutical Benefits Scheme (PBS) for all citizens. Decisions on drug subsidy are based on assessment by the Pharmaceutical Benefits Advisory Committee (PBAC), which evaluates incremental effectiveness and cost-effectiveness of the medicine. The PBS has recently introduced significant developments to maintain the ability of this national system to subsidise access to needed, effective and safe medicines at a price individuals and the community can bear in the face of rapidly escalating costs of new drugs, particularly high cost biopharmaceuticals.

Access to high cost medicines (HCMs) under the PBS is tightly regulated, requiring an "authority" for prescribing to ensure their cost-effective use. This authority is given if the patient meets strict eligibility criteria usually comprised of clinical and

laboratory based measures. This approach thereby targets a subgroup of patients who are likely to benefit most, based on clinical and cost-effectiveness evidence. Increasingly, there is collaboration between the PBAC, the sponsoring pharmaceutical companies, and medical specialist organisations to achieve agreed outcomes. A representative example of this emerging approach is the controlled access to biological drugs (etanercept, infliximab, adalimumab, and anakinra) for the treatment of rheumatoid arthritis. The *stakeholder consultation* process that contributed to the decision to subsidise anti-rheumatic biologicals set a new paradigm for analogous PBS decisions on HCMs. When resources are constrained, restricting access is inevitable, but such developments must be monitored, assessed, and analysed.

This research program examined the current system of access to HCMs in Australia via the PBS, with a focus on the anti-rheumatic biologicals. The principal purpose of this research was to contribute to the knowledge and understanding of managing access to expensive medicines and ways in which systems of access could be improved.

There are a total of eight chapters in this thesis. Chapters 1 and 2 present an overview of the literature on access to medicines. More specifically, Chapter 1 provides an overview of the literature with the purpose of summarising the principles, issues and challenges relating to this topic: (i) the components of a national medicines policy for supporting access to medicines within a healthcare system, (ii) the common challenges faced by many countries to provide medicines, (iii) various methods of drug cost-containment, and (iv) the recent challenges posed by the introduction of HCMs, notably the "biopharmaceuticals". Chapter 2 presents the

background to the controlled access to HCMs under Australia's PBS. This includes an overview of various mechanisms of access to medicines in Australia. The access arrangements for anti-rheumatic biologicals, a representative example of the evolving approach to this issue, are described in detail. Australia's National Medicines Policy and the principles of Quality Use of Medicines, the framework for the subsequent research in this thesis, are also outlined in Chapter 2.

Chapters 3 to 6 report on the results of a detailed examination of the access to anti-rheumatic biologicals via the PBS. Qualitative and quantitative methods were employed. Chapter 3 describes an in-depth qualitative investigation of the access to biologicals. This study was based on interviewing a wide range of relevant stakeholders (rheumatologists, patients, government advisors, public servants, consumer representatives, and pharmaceutical industry spokespersons). Stakeholders' perceptions and experiences regarding the access to biologicals, and their opinions on the collaboration between stakeholders were explored.

Chapters 4 to 6 are based on three studies which form part of a quantitative evaluation of the access scheme for biologicals. Chapter 4 examines the challenges of accessing secondary data in Australia, and describes an attempt to examine the impact of the PBS access scheme for anti-rheumatic biologicals using a national administrative data set. Approaches used by other countries to monitor health outcomes of patients treated with biologicals and the lessons for Australia are also discussed in Chapter 4. Chapter 5 describes the utilisation pattern of biologicals under the PBS and the associated government expenditure, using population level, aggregated claims data. Chapter 6 reports a study examining changes in prescribing of conventional disease-modifying anti-rheumatic drugs before and after the

availability of biologicals under the PBS in August 2003, using national aggregated dispensing data.

The access scheme for HCMs under the PBS is examined from an ethical perspective, using primarily a framework grounded in procedural justice and emphasises democratic deliberation, the "accountability for reasonableness" framework. This analysis reported in Chapter 7 was conducted as a pertinent component of this evaluation of access to biologicals. The processes of decision-making and implementation of PBS criteria for anti-rheumatic biologicals were focused upon. Approaches to optimise individual patient outcomes clinically and ethically despite accepted resource constraints are proposed.

Chapter 8 discusses the relevance and significance of the studies described in this thesis in light of the National Medicines Policy framework and Quality Use of Medicines Strategy. This final chapter also highlights critical areas where improvements are possible to strengthen access to HCMs under the PBS. Future directions of research on this subject are proposed.

Australia's PBS, like drug subsidy programs in other countries, is adapting to changing healthcare needs including access to HCMs. The studies undertaken in this thesis make a significant contribution to understanding how access to HCMs is currently being managed under the PBS in Australia. Findings from this work raise important issues that decision makers need to consider and to address appropriately and in a timely fashion regarding the principles and processes that underpin equitable, efficient, and effective access to expensive medicines under subsidy systems. Results of this research can be used to guide future processes and

policies on managing and improving access to HCMs in the interest of optimal health and economic outcomes of all stakeholders, particularly patients. At the same time, targeted access to highly specialised, costly medicines warrants further study with respect to the effectiveness, dynamics, and sustainability of nationally subsidised access programs such as the Pharmaceutical Benefits Scheme.

1. ACCESS TO MEDICINES

In this chapter, an overview of the literature on access to medicines is presented, from an international perspective, with the purpose of summarising the principles, issues and challenges relating to this topic. The overview includes a description of the components of a national medicines policy for supporting access to medicines within a healthcare system, and the common challenges faced by many countries to provide medicines. Various methods of drug cost-containment are outlined. The recent challenges posed by the introduction of expensive medicines, notably the "biopharmaceuticals", are also described within this context.

1.1 Introduction

Medicines can save lives, prevent and cure diseases, and help people avoid disability.(2) When medicines are available, affordable, safe, efficacious, and appropriately used, they reduce debilitation from chronic diseases, enhance quality of life for patients and carers, increase independence, and reduce the overall costs of treatment.(2) Therefore, medicines play an important role in healthcare. International experience has shown that the provision of prescription drugs can be an important contributor to population health. A positive correlation between increased life expectancy and increased pharmaceutical consumption has been reported in a study focused on the healthcare consumption and health outcomes in 21 Organisation for Economic Cooperation and Development (OECD) countries.(3)

1.2   Access to medicines

Access to health care, including 'essential' medicines, is regarded as a human right by the International Covenant on Economic, Social and Cultural Rights.(4) Although some consider it an aspiration, and that civil and political rights are of higher priority (the International Covenant on Civil and Political Rights), access to essential medicines is supported widely by many countries, including Australia, as part of the fulfilment of the right to the 'highest attainable standard of physical and mental health' – article 12 of the International Covenant on Economic, Social and Cultural Rights (http://www.unhchr.ch/html/menu3/b/a_cescr.htm). In relation to the same Article, the concept of essential medicines was introduced by the World Health Organisation (WHO) in stating that: "essential medicines are those that satisfy priority health care needs of the population". This concept considers new therapeutic options and changing therapeutic needs.(4) Access to essential medicines is a critical component of healthcare systems. Which medicines are regarded as "essential" is dependent upon the priorities set by each individual healthcare system.(5)

The definition of "timeliness" with respect to access to medicines is relevant to the present work. However, the concept of "timely access to medicines" has not yet been clearly defined internationally. Broadly, "timeliness", with respect to access to healthcare and taking a patient-centred approach, is a dimension of quality that relates to whether care is available and the capacity of the health system to provide care to the patient when need is recognised within a reasonable period given all the factors that might influence that time.(6-8) Timely delivery of care has the potential to reduce mortality, morbidity, and long-term disability for chronic medical conditions while a lack of timeliness can result in emotional distress, physical harm and

financial burden for patients.(8) Generally, the time to affordable access to medicines for the majority of patients are influenced by: (i) application for registration to gain licensing approval by regulatory authorities; and (ii) application for reimbursement of the cost of the medicine by insurers and payers as well as any factors potentially impacting on these two stages e.g. price negotiations (further discussion on this topic with respect to the Australian situation appears in Chapter 2).

Efforts by the WHO focus on three major objectives of national drug policies to promote equity and sustainability of the pharmaceutical sector (Table 1.1) (9):

- Access – equitable availability and affordability of essential drugs,

- Quality – the quality, safety and efficacy of all medicines, and

- Rational use – the promotion of therapeutically sound and cost-effective use of drugs by health professionals and consumers.

Table 1.1 Components of a national drug policy as recommended by World Health Organisation (9)

	Access	Quality of drug	Rational use
Selection of essential drugs	✓	Indirectly linked	✓
Affordability	✓		
Drug financing	✓		
Supply systems	✓		Indirectly linked
Regulation and quality assurance		✓	✓
Rational use			✓
Research	✓	✓	✓
Human resources	✓	✓	✓
Monitoring and evaluation	✓	✓	✓

As of 2002, over 100 countries had national medicines policies in place or under development, more than 150 countries had a national or regional "essential" medicines list, and about 130 countries had developed national treatment guidelines to promote rational use of medicines.(10) Access to medicines depends on four critical and interdependent components: rational selection of a range of "essential" drugs, affordable prices, sustainable financing, and reliable supply systems (Table 1.1).(11) A brief description of these components as recommended by the WHO now follows.

1.2.1 Selection of medicines

Safety, efficacy, quality of medicines, and increasingly their comparative cost-effectiveness (public health value or "value for money") are assessed by each country aspiring to the International Covenant, as noted, to produce selective national, provincial, or state lists of essential medicines and vaccines. These pharmaceuticals are the basis for procurement, reimbursement, and use in clinical practice.(9, 11)

1.2.2 Affordable prices

Affordable prices are important if there is to be access to medicines through public and private sectors. Competition lowers prices.(2) Due to the lack of a fixed, international price for a medicine, best prices for pharmaceuticals for insurers and third party payers may be aided by: availability of price information which helps payers in price negotiations, generic competition for off-patent medicines, competition among therapeutic substitutes, bulk procurement, reduction of taxes and duties on medicines, improved distribution efficiency, and reasonable

dispensing fees.(2, 12) Prices of newer medicines have been of particular concern as they are unaffordable in many health systems around the world. It is essential to obtain a right balance between incentives for innovation and assurance of affordability.(12) In many developing countries, where payment for medicines is largely out-of-pocket and health insurance is rare, high prices deny patients access to medicines.

1.2.2.1 Intellectual Property and Trade Agreements

Patents for pharmaceutical products are now regulated by the Trade-Related Intellectual Property Rights Agreement (TRIPS), which was a part of the World Trade Agreement that came into effect in 1995. All Member States of the World Trade Organisation must abide by this agreement. Patent protection is crucial for the economic viability of industry and provides important incentives for the research and development of new drugs. The TRIPS agreement imposed global minimum standards on Intellectual Property Rights, including patent protection for 20 years from the date that the patent is filed. The provisions of Intellectual Property Protection have an impact on affordability and access to pharmaceuticals (medicines and vaccines), particularly newly patented pharmaceuticals in developing countries, restricting them from producing or buying generic equivalents that usually cost much less than branded products.(13) For example, a concern about the implementation of TRIPS was the potential loss of affordable access to anti-retroviral medicines for treating human immunodeficiency virus/acquired immunodeficiency syndrome, particularly in low- and middle-income countries.(11) To deal with this, under TRIPS, flexibilities, such as parallel importation and compulsory licensing (a licence granted to work the invention without the authorisation of the patent holder), are permitted for developing countries to

enhance access to pharmaceuticals deemed necessary to protect public health. National legal mechanisms are invoked in this situation.(14) Also, the least developed countries are permitted to delay enforcement of patent and data protections until 2016.(13)

Bilateral and free trade agreements negotiated outside the World Trade Organisation may also impact on access to medicines. These agreements may include additional standards such as patent term extension beyond the 20-year term required by the TRIPS agreement; exclusivity of test data on drug efficacy and safety for at least 5 years irrespective of whether it is patented or not (i.e. no other individual or company would be able to use the test data without consent of the originator); the linkage between drug registration and patent protection (the relevant national health authority must deny marketing approval to a generic version of a product if a patent is in force); and in some cases, limitations to the grounds for granting compulsory licences and parallel importation which are important for promoting access to medicines at affordable prices.(13) The free trade agreement between Australia and the United States of America (USA) became effective from 1 January 2005. Throughout the negotiations, there was intense debate and concern about ongoing affordable access to medicines and population health because the Pharmaceutical Benefits Scheme (PBS) – Australia's national drug subsidy program – was included in this free trade agreement.(15) As part of the finalised agreement, the Australian government is committed to make improvements to the transparency and timeliness in the evaluation of drugs for inclusion in the PBS, and establish an appeal mechanism for denied applications. A research project is in progress to examine the effects of this trade agreement on PBS processes (including impact on regulatory structure and PBS processes, drug availability, and drug utilisation and affordability).(15)

1.2.3 Sustainable and adequate financing

Fair and adequate financing for medicines depends on multiple sources: government funding, social and private health insurance including drug benefits, and contributions by employers in health and drug financing. Patient cost-sharing can complement these sources of funding.(2, 12) Patient cost-sharing as an intervention to contain drug expenditure is discussed further in a later section of this chapter (Section 1.5). Further, 'risk sharing' financial arrangements between payers and the pharmaceutical industry are used to establish payer provision of medicines because confidence is raised that unanticipated errors in cost or profit projections will be hedged and to allow reasonable profits to the pharmaceutical industry (discussed subsequently in Sections 1.5 and 1.7.3).

1.2.4 Reliable health care and supply systems

Adequate levels of medical and pharmaceutical services are essential for public health. These include affordable and reliable diagnostic tests, and appropriate access to well-educated clinicians, pharmacists, nurses and other health professionals and to facilities related to the treatment.(2) Reliable access to medicines depends on well-functioning regulatory control and pharmaceutical distribution systems that are reliable and efficient (Table 1.1) – that is, that provide a consistent supply of medicines, as well as the ability to assure product quality (including appropriate storage conditions).(11) Regional purchasing schemes, regulatory authorities, pharmaceutical industry, distributors, and health professionals are some of the important players in the supply chain.

1.2.5 Rational use of medicines

Access to medicines is a vital pre-requisite for rational use of medicines (Table 1.1). Lack of access to medicines and irrational (or non-rational) use of medicines may result in serious morbidity and mortality.(16) Efforts to promote rational prescribing and use of medicines have been made since a WHO conference in 1985 in Nairobi.(17) "Rational use of medicines" means that patients receive appropriate medicines and doses according to their clinical and individual needs for an adequate treatment period, and at a reasonable and affordable cost to them and the community.(9) Research collaboration between WHO, the International Network for the Rational Use of Drugs and other organisations has focused on studying interventions to promote rational use of medicines.(17) Recommendations by WHO on how to promote rational drug use include: development and use of evidence-based clinical guidelines, establishment of drugs and therapeutics committees, education and training of healthcare professionals, responsible drug promotion, independent medicine information, consumer education and consumer engagement, regulatory strategies to support rational use of medicines, and development and use of indicators to monitor effects of fundamental changes occurring in health systems.(9, 17)

1.2.6 Resources

Effective drug regulation to ensure the quality of medicines requires a combination of technical, human, financial, and organisational resources as well as legal framework.(18) Development of human resources is a component of a national drug policy, as recommended by the WHO (Table 1.1). Government should be committed to ensure that there are enough trained and motivated personnel to implement components of the policy.(9) Investment in other resources, such as health

information systems, is also recognised as an additional, important component. Timely availability of sound data is critical for health policy decision-making. The role of health information systems is to generate, analyse and disseminate such data.(19)

1.2.7 Monitoring, Evaluation, and Research

Monitoring and evaluation are also WHO recommended components of a national drug policy (Table 1.1). Governments should be committed to support these activities. Independent, external evaluation of the impact of policies on clinical and economic outcomes should also be promoted.(9)

Research is important to facilitate the implementation, monitoring and evaluation of different aspects of a national drug policy (Table 1.1). It is essential to assess the policy impact on health systems and delivery, to study the economics of drug supply, to identify problems related to prescribing and dispensing, and to understand the social-cultural aspects of drug use.(9)

1.3   Health care expenditure

Approaches to healthcare funding to protect patients from excessively high costs for care and treatment differ from country to country. There are three main approaches to funding healthcare in developed countries: (i) General taxation: in countries such as the United Kingdom (UK) and Sweden there is universal coverage by a single payer, and health providers are salaried or capitated; while in countries such as Australia and Canada there is universal coverage by a single payer, and health providers are paid a fee for each service; (ii) Social health insurance, in countries such as Germany, France, the Netherlands, Japan and Singapore, delivers

universal coverage by multiple funds or insurance carriers, and health providers in the public sector are salaried or paid a fee for each service in the private sector; and (iii) Major contributions from voluntary insurance with multiple payers and providers, delivered through different systems and payment strategies, is the approach taken in the USA.(20, 21)

Expenditure associated with healthcare delivery has increased dramatically in most developed countries over recent decades. In developed countries that are members of the OECD, the public sector is the main source of funds for health services. In 2003, 67.5% of health expenditure in Australia was publicly funded, lower than the average of 73% for OECD countries. By comparison, a relatively high (>80%) share of health service costs came from public spending in comparable countries such as the UK, Denmark, Norway, Sweden and Japan; while the USA had the lowest public share of health expenditure (45%).(22) Total health expenditure accounted for 9.2% of Gross Domestic Product (GDP) in Australia in 2003, higher than the average of 8.9% in OECD countries, but lower than a number of countries such as Switzerland (11.6%), Germany (10.9%), France (10.5%), Canada (9.9%) and the USA (15.3%) – which spent the highest percent of GDP on health (Table 1.2).(22) Growth in healthcare expenditure in recent years is partly due to new medical technologies and the introduction of new and more expensive pharmaceuticals and an ageing population (discussed subsequently in Section 1.3.2). The price of new medications continues to increase and expenditure on pharmaceuticals is consuming a growing percentage of the total healthcare expenditure in many countries.(23)

Table 1.2 Health expenditure in OECD countries in 2004 (22)

Country	Public share (% of health expenditure)	Drug spending (% of total health expenditure)	Health expenditure (% of GDP)
Australia	**67.5**	**14.2**	**9.2**
Canada	70.0	17.7	9.9
France	78.4	18.9	10.5
Germany	78.2	14.6	10.9
Japan	81.5	18.9	8.0
Netherlands	62.3	11.5	9.2
OECD	72.9	17.7	8.9
Sweden	85.0	12.3	9.1
Switzerland	58.4	10.4	11.6
United Kingdom	86.0	15.8	8.3
United States	45.0	12.3	15.3

Note: figures have not been adjusted for purchasing power parity.

1.3.1 Pharmaceutical expenditure

The rise in expenditure on pharmaceuticals, by an average of 32% in real terms between 1998 and 2003, has been one of the factors behind the rise in total health spending in OECD countries. Growth in pharmaceutical spending has outpaced total health expenditure.(23) Spending on drugs accounted for an average of 17.7% of total health expenditure in OECD countries in 2004. The top five spenders on pharmaceuticals as a percentage of total health spending were Slovak Republic (38.5%), Korea (28.8%), Hungary (27.6%), Turkey (24.8%), and Italy (22.1%).(23) Health spending as a share of GDP ranges widely between countries (8.0% to 15.3%), as shown in Table 1.2. Australia spends a similar proportion of health expenditure on drugs as a number of European countries (Table 1.2). In 2002, spending on pharmaceuticals accounted for 14.2% of total health spending in Australia, up from 12.6% in 1999 and 11.0% in 1994.(22)

In 2003, total drug expenditure per person was highest in the USA (more than US$700/person), followed by France (about US$600/person), Canada and Italy (about US$500/person). Drug expenditure per capita in Australia is about US$350/person, slightly below the average of US$366/person for OECD countries. Variations in pharmaceutical expenditure across countries reflect differences in government policies, prices and consumption, income levels, as well as the pace of introduction of new and often more expensive drugs.(23)

1.3.2 Factors contributing to growth in pharmaceutical expenditure

A combination of many factors has contributed to the growth in pharmaceutical expenditure in many countries, including Australia. The major determinants are: drug price inflation; an increase in the proportion of the elderly population which is more likely to require multiple drug therapy; changes in patterns of medicine use such as substitution of less expensive, older treatments by more expensive, newer therapies; increasing number of available drug interventions such as those for long-term prevention in conditions e.g. osteoporosis and hyperlipidaemia; the introduction of new, more effective and more expensive drugs; and an increase in health expectation and demand by patients and society.(24-27) Studies affirm that growth in the proportion of the elderly in the population adds to the rising utilisation of healthcare resources and overall health expenditure.(26, 28, 29) However, the increase in drug spending due to the growth in the proportion of elderly population is small compared to recently observed increases in overall pharmaceutical expenditure.(29)

Substitution of older less expensive agents with more expensive new therapies has been a major driver of increased pharmaceutical expenditure. Many of these new agents are modifications (e.g. changes in relation to dose form or route of

administration), combinations of already existing molecules, new members of the same class of drugs already marketed (commonly known as "me-too" drugs), and enantiomers of previously registered racemates rather than "breakthrough" agents.(30) Higher acquisition costs of new medicines sought by the pharmaceutical industry are partly due to the significant investment that goes into drug research and development,(31) and the costs of submissions to regulatory authorities. However, non-breakthrough new medicines are less valuable than breakthrough medicines and prices should reflect this contrast in value. It should also be acknowledged that public funded biomedical research has been the source of many breakthrough medicines (32) but the public outlays are not obviously recognised in the price ultimately paid for the medicine by the patient or payer. New therapies are often adopted because of reports of an improved aspect of treatment (e.g. less frequent administration, lower incidence of adverse events, better compliance, less interactions than other medicines in the therapeutic group) rather than significant differences in pharmacological effectiveness.(33) Freedom of choice for patients and doctors may be a determinant of greater drug expenditure.(34) Marketing strategies and direct-to-consumer advertising[1] also increases demand for expensive, branded medications, thus influencing pharmaceutical expenditure.(35) For example, it has been reported that direct-to-consumer advertising is an important predictor of switching among proton pump inhibitors.(36) In addition, the pharmaceutical industry is known to promote particular diseases to prescribers and consumers, these often being new and verging on part of the normal human experience. Such forms of medicalisation of previously considered features of normality have been described as "disease mongering" and lead to a widening of the boundaries of treatable illness in order to expand markets for new products. This important phenomenon, that is not easy to

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[1] Direct-to-consumer advertising is not legal in Australia.

evaluate with respect to risks and benefits, is known to affect pharmaceutical expenditure.(37)

Rising expenditure is a challenge to healthcare systems because there may be an opportunity cost if the expenditure on medicines could be used in other ways to better improve population health. Further, high prices represent budgetary pressure on payers who try to maintain access to medicines for the population at an affordable cost. Faced with this challenge, healthcare systems have adopted a variety of approaches to sustain the systems, including "priority setting" and strategies to contain drug expenditure.

1.4   Priority setting in health care

Every healthcare system faces some level of scarcity in resources, thus not everyone who needs (or wants) a particular form of health care can gain access to it. How resources should be allocated to health care including drugs is a very specific example of the general problem of distributive justice.(38) Issues related to justice in health care can be divided into two dimensions: allocation and access.(38, 39) "Allocation" refers to determining what resources should be devoted to health care and "access" refers to whether people who are (or should be) entitled to health care services receive them.(39) Decision-making has been described as "a process by which a person, group, or organisation identifies a choice of judgement to be made, gathers and evaluates information about alternatives, and selects from among alternatives".(40) Healthcare decision-making is more difficult and complex when resources are scarce.(41, 42)

Allocating resources is also known as "priority setting" or "rationing". These terms have been used interchangeably in the literature. "Priority setting" has a more positive connotation than "rationing"; "rationing" implies denial or delay of access to healthcare resources.(43, 44) More recently, the term "sustainability" has also been suggested.(45) Regardless of the term used, the concept relates to assigning priorities, that is, 'determining who gets what and at whose expense'.(46) It involves judgement informed by evidence to balance competing goals and values (e.g. equity versus efficiency) in the context of multiple stakeholder relationships, limited resources, and political influences.(47, 48) It follows that "accountability" is an important, relevant issue in priority setting.(48) Accountability has been described as entailing the procedures and processes by which one party provides justifications and takes responsibilities for its actions and decisions.(49)

At a national, governmental level, policy decisions are made about the allocation of resources to specific sectors or groups within a healthcare system.(50) Decisions at this level are often based on medical need (the severity of the condition), or the appropriateness of healthcare interventions (the effectiveness and cost-effectiveness), or both.(51) An example of such decision-making is the process required to assess pharmaceuticals for subsidisation under the PBS by the Pharmaceutical Benefits Advisory Committee in Australia. Assessment of medicines prior to entry into drug formularies is now increasingly used and, in many countries, a mandatory requirement (further discussed in Section 1.5.2). Agreement should be reached on notions such as "health", "quality of life", and "necessary care" before assessments of effectiveness and cost-effectiveness is proposed.(51) However, it has been argued that because there are no simple or technical solutions that may help decision makers in the allocation of limited healthcare resources,(52-54) the

focus should, therefore, be on the decision-making process and securing legitimacy for decisions made.(55, 56)

Priority setting decisions are also made at an institutional level, include those made by hospitals,(57) for example, decisions about the allocation of hospital budgets.(58) Most decisions on which medicines are to be made available and how much resources to be allocated to specific medicines in hospitals are undertaken by hospital Drug and Therapeutic Committees (DTCs).(59, 60) Hospital DTCs have been described as "policy makers at the institutional level for ensuring expenditure on medicines provides good value".(61) DTCs are also responsible for containing costs of medicines and ensuring the rational use of medicines. Useful studies examining priority setting processes in various healthcare settings around new technologies and medicines have been conducted, including pharmacy benefit management organisations,(62) intensive care units,(63) hospitals,(64-66) and cancer care organisations.(67-69) More recently, a similar study has also been conducted examining decision-making processes to allocate resources to expensive medicines in Australian public hospitals.(46) However, there is a paucity of literature on priority setting processes around new technologies, including medicines, at a national, governmental level.

1.5   Methods of drug-cost containment

The expenditure on prescription medicines is a major focus of cost control by public and private health systems because spending on pharmaceuticals represents a sizable and increasing proportion of health expenditure, as noted, and pharmaceutical expenditure is a clearly defined segment that can be more easily identified, measured, and evaluated in comparison to the expenditure on health

professional services.(70) Various cost-containment policies have been established in many countries, primarily focused on public financing of prescription medicines in ambulatory care. The main purposes of these interventions are to better manage escalating pharmaceutical prices and expenditure, and to influence drug prescribing to achieve a more cost-effective use of therapies (including the objective of reducing unnecessary utilisation of drugs). These approaches intended to improve the efficiency of pharmaceutical services affect patients' access to medicines, directly and/or indirectly. This section summarises the various methods of drug cost-containment, focusing on approaches used at a national level.

1.5.1 Drug pricing policies

The price of medicines affects their availability and affordability, and these are major determinants of access to medicines. Pricing policies of governments and other payers focus on keeping prices as low as possible and, thereby, improve access to medicines. Prices are usually determined on the basis of the perceived or estimated therapeutic value of the drug, the comparative effectiveness of the new drug over existing products, prices charged for the same product in other countries, and potential benefits to the economy.(70) Policies include: control of product reimbursement price (reference pricing and generic substitution), direct control of product price and profit, and price reductions for exceeding an agreed level of sales.(70, 71)

1.5.1.1 Reference-based pricing

Reference pricing is a mechanism to encourage use of the less expensive agents that are fully reimbursed. Many countries use international price comparison ('international benchmarking') as the basis for reference pricing, which is a useful method when applied across comparable countries with similar purchasing power.(72) Reference pricing is based on the assumption that drugs within a specific class are interchangeable and that a common reimbursement level can be established.(33) Pharmaceutical manufacturers are free to set any price for their products, but have a strong incentive to set prices not considerably different to the reference price – ceilings set by payers that cover drugs up to the reference price – so to compete with already reimbursed drugs sharing the same market.(33, 73) The patient is required to pay the difference if the chosen medicine is at a cost above the reference level. The reference price may be the average price of drugs in a category, the lowest priced drug, or the lowest priced generic drug plus some amount (e.g. 10% in Sweden).(74) This method mainly affects two of the major drivers that increase pharmaceutical expenditure, that is, price inflation and substitution of older less expensive treatments by newer more expensive therapies. Studies have reported that a reference pricing scheme is an effective tool for price control in the short-term, as has been demonstrated, for example, in Germany and the Netherlands.(75, 76) However, little is known about the effects of reference pricing on patient health or substitution with other interventions, and expenditure on the entire health system.(77, 78) A study suggested that physicians in Germany may have responded to the reference pricing scheme by increasing their rate of patient referrals to hospitals.(79) Net savings of these policies may be reduced if healthcare costs in other sectors increase. Reference pricing policy has been shown to be effective in reducing expenditure on angiotensin-converting-enzyme inhibitors in Canada, however, in patients who switched therapy, there was a moderate increase

in the number of visits to physicians and hospitals in the time immediately following the switching.(80)

Australia introduced the Therapeutic Group Premium Scheme (drugs are grouped with related but not chemically identical drugs for same therapeutic uses, e.g. angiotensin-converting enzyme inhibitors) in 1998 under the PBS.(33) The Pharmaceutical Benefits Pricing Authority (PBPA) has the task of negotiating prices for new medicines with pharmaceutical suppliers and reviewing prices of PBS-subsidised products. In this work PBPA takes into consideration overseas prices.(81)

The main argument against reference pricing is its potential to act as a disincentive to pharmaceutical innovation, namely improving upon existing drugs and developing new ones.(33, 82) In Australia, there is some industry protection through the Pharmaceutical Industry Investment Program which was designed to provide partial compensation to industry for the price suppression of medicines on the PBS.(83)

1.5.1.2   Generic substitution

The use of generic drugs is encouraged in many countries, for example, Germany, Denmark, Finland, France, Spain, the Netherlands, Switzerland, and the USA.(74) Generic substitution has been demonstrated to contain costs in the short-term in Germany.(70) Reference-based pricing and generic substitution policies have similar aims, that is, to contain the rate of growth of drug costs by increasing the market penetration of cheaper generic drugs, or by encouraging price reductions of the new brands.

In Australia, the Minimum Pricing Policy (or the Brand Premium Policy) was introduced into the PBS in 1990. This policy involves grouping of drugs which have the identical bioactive ingredient and are shown to be therapeutically interchangeable or bioequivalent, and sets the government subsidy for a drug at the level of the lowest priced brand (the benchmark price).(84) The benchmark price is the lowest weighted average monthly treatment cost (WAMTC). The monthly treatment cost of drugs is calculated, compared, and weighted by dosage, strength and volume for the latest 12-month period so that the cost per month is equivalent for drugs which are therapeutically equivalent.(85) In 1994, (four-years after the introduction of this policy) there was only a small proportion of prescriptions (17%) dispensed for generic products. Generic substitution by pharmacists was subsequently permitted from 1994.(84) Pharmacists have an economic incentive to dispense generics (if not disallowed by the prescribing doctor) because of supplier discounts and intense marketing efforts by the generic pharmaceutical industry.(86) The effect of generic substitution at the pharmacist level has resulted in a marked increase in the use of generic-brand medicines. The market share of generic brands had increased to 45% in 1999.(84)

1.5.1.3 Direct price and profit controls

Direct price controls involve the practice of fixing the price of a pharmaceutical. This approach is used by some countries to supplement reimbursement pricing systems. For example, prices of all pharmaceuticals (both reimbursable and non-reimbursable products) must be approved by governments in Spain and Belgium before marketing.(71) Prices may be fixed at market entry and either frozen or increased at a fixed rate afterwards with adjustment for inflation. The prices of medicines can be controlled at the ex-factory, wholesale and pharmacy levels. Usually the wholesale

and pharmacy margins are also controlled.(70) Most governments in Western European countries have defined profit margins for drug wholesalers and retailers to facilitate the control of prices. As a consequence of various price regulations, prices of medicines vary considerably across Europe,(70) including the wholesale and pharmacy retail prices of innovative medicines.(87)

In Australia, the PBPA may also set drug prices by "cost plus method", that is, the price is equal to the cost of manufacture plus a margin. This method is usually used to set prices for stand-alone products, or when recommending a benchmark price for a therapeutic group.(81) Other costs such as the remuneration that pharmacists will receive for dispensing PBS medicines, the wholesaler mark-up, the pharmacist mark-up and handling fees are governed by the Community Pharmacy Agreement between the Commonwealth Government and the Pharmacy Guild of Australia.(88) Within this Agreement, pharmaceutical wholesalers receive payments from the Government to deliver the full range of PBS medicines to all pharmacies, regardless of location and usually within the next business day to ensure that Australians have access to pharmacy services and PBS medicines.(88)

Profit controls are used in the UK. Under the Pharmaceutical Price Regulation Scheme, voluntary agreements are made between the Department of Health and the pharmaceutical industry. The aim is to obtain drugs at reasonable prices while promoting a strong pharmaceutical industry. Profits made by pharmaceutical companies from drug sales to the National Health Service are monitored and the permitted rate of return on capital is around 17-21%.(70, 89) Some have argued that this Scheme has done little to control drug prices for the National Health Service,(90) because the drug budget has increased steadily (by approximately 10% per year

between 1967 and 1997),(91) and drug prices in the UK are among the highest in European countries.(92) This method is also used in Spain with the margin for profits set around 12-18%.(70, 74)

1.5.1.4 *Volume related price regulation*

Volume related price reduction is an approach under which the government imposes a fixed budget on pharmaceutical expenditure. If this budget is exceeded, the pharmaceutical industry must partially refund the health insurance funds. This method has been used in countries such as the UK, France, Germany, Italy and Spain.(71, 74) Regulation of promotional activities potentially helps to control volume of sales. For example, a fiscal incentive in the form of a sliding-scale tax based on the level of promotion expenditure is used in France.(93) Price-volume arrangements (also called risk sharing arrangements) between the Commonwealth Department of Health and the pharmaceutical industry are also used in Australia to fund drugs where significant uptake is likely, where there is uncertainty about future usage, or concern about usage outside the subsidised indications leading to greater uptake than predicted.(85, 94)

1.5.2 Selection of medicines for reimbursement

As payers of healthcare cannot afford to provide every medicine for all citizens without limitations, challenging choices between competing healthcare products becomes inevitable. While medicines are licensed for sale based on evidence of safety and efficacy versus a placebo, increasingly payers require additional evidence of clinical- and cost-effectiveness compared to existing therapies to determine whether the new products will be reimbursed. The main focus of controls

on drug reimbursement is to increase the cost-effectiveness of the use of medicines. This is mainly through national and institutional drug formularies that 'list' cost-effective medicines.

1.5.2.1 Drug formulary

A common method of cost containment used by the vast majority of healthcare systems in which there is a central revenue base is priority setting or restricting access to a selected list of medicines. In particular, in government-funded healthcare systems, the list of selected medicines may be in the form of: (i) "positive lists" – lists that include selected drugs for public reimbursement, in countries for example, Australia, Italy, France, and New Zealand; or (ii) "negative" lists – lists of drugs that will not be publicly reimbursed, in countries for example, the Netherlands, Ireland, Germany, and the UK.(95, 96) Positive or negative lists were introduced in the 1980s as interventions to reduce the demand for drugs. In most countries, such lists are generally revised several times a year by government bodies. The decisions regarding drug inclusion or exclusion are based variously on safety, efficacy, cost utility, cost-effectiveness, professional opinion, and, to some extent, political considerations.(74, 97-101)

In the USA, studies have found that drug formulary may shift prescribing behavior toward the selected drugs,(102) and an association between restrictive formularies and smaller increases in drug utilisation and expenditure.(103) Many state Medicaid programs (which fund healthcare services for the indigent and elderly) have developed lists of preferred drugs for which there is reimbursement – generally these include generic drugs and medicines that are less costly than others in the same class. Medicines not on the list usually require prior-authorisation (discussion in Section

1.5.3.4) in order to be reimbursed. However, data on the risks and benefits of restrictive drug formularies to patients have been scant.(104) Further, withdrawing a medicine from reimbursement may lead to unexpected and unwanted outcomes. In a study of the withdrawal of drugs with questionable efficacy in a random Medicaid sample, Soumerai and colleagues demonstrated that withdrawing reimbursement resulted in an increase in prescriptions overall due to substitutions, many of which were not desirable.(105) Such potential impacts on the use of other prescription drugs and health outcomes should be considered by all stakeholders, particularly by policy markers.

1.5.2.2 Economic evaluation

Access to medicines is increasingly influenced by population-based analyses of the relative economic value of the medicine to the community. Economic evaluations that examine the long-term costs and health impact of drug therapies have become an important factor for reimbursement decision-making during the last two decades. Australia was the first country to introduce a mandatory requirement for economic analysis to select pharmaceuticals for a publicly funded formulary in 1993.(106) Use of economic evaluation has been adopted globally. Many countries have formal procedures for reviewing the information about the cost-effectiveness ("value for money") of new drugs, and incorporating it into decisions about reimbursement, pricing and treatment guidelines,(78, 107) including, for example, Canada, New Zealand, and a number of countries in Europe – the UK, France, Spain, Sweden, Finland, Portugal, and the Netherlands.(97, 108) Making decisions regarding the reimbursement price that a government or insurer is willing to pay for an innovative drug based on evidence of cost-effectiveness, in principle allows a wide range of costs and benefits to be considered. This compares favourably with the heretofore

common approach of focusing on drug acquisition costs alone. It has been argued that a well-conducted economic analysis should provide a balanced, and explicit representation of the disease in a simulation model that captures the essence of the disease in real-world circumstances in a reasonable timeframe, and enables comparison of relevant outcomes and treatment consequences (costs and effectiveness) of two or more interventions.(109) It is important to note that decisions on the appropriate use of new treatments are often based on inadequate data because early clinical studies provide data on efficacy but leave substantial uncertainty around the effectiveness of the medicine (further discussed in Section 1.7.1). Incremental cost-effectiveness expresses the relationship between the extra costs and additional benefits of a new treatment in comparison with a common standard treatment that it might replace, and determines whether a product represents value for money at the price sought. New drugs with no demonstrable advantage over existing treatments are offered the same price under this approach ("cost-minimisation"). Quality-adjusted life-years (QALYs) is a useful quality of life measure that aggregates all health consequences, both good and bad in a single value, and enables comparison across diseases. Economic analysis may empower payers, physicians and patients to choose the most clinically and economically efficient medicines, even if they have high prices. As healthcare resources are scarce, economic evaluation helps to maximise health benefits attainable for a population and to achieve overall efficiency. This is an approach for deploying limited resources in a manner that provides access to medicines for the majority. However, economic evaluation operates under this goal even if this is achieved by offering the benefits (e.g. access to medicines) to only a portion of a population that might benefit from it.(110) Therefore, the method of economic evaluation has been criticised for focusing primarily on efficiency with limited consideration of equity that emphasises distributing benefits equally across a population.(110)

1.5.3 Interventions for influencing prescribing

Prescribing decisions are influenced by many factors including the prescribing physician, the patient, the physician-patient interaction, and the wider social context such as the effect of advertising and promotion of the products by manufacturers and the financial incentives and disincentives for all parties. Patients' expectations and their degree of knowledge of their diseases seem to be important factors influencing the prescribing rate.(111) Changing prescribing behaviour is difficult to achieve and often requires multifaceted interventions.(112, 113)

Australia has a National Medicines Policy, within which is the important concept of Quality Use of Medicines (further discussed in Chapter 2).(114) The Quality Use of Medicines (QUM) initiative was introduced in Australia by the federal government in 1992.(115) QUM is defined as: judicious selection of management options (including non-pharmacological alternatives), appropriate choice of medicines if a medicine is considered necessary, and safe and effective use of medicines.(116) The primary aims of QUM are to promote quality, evidence-based prescribing, and to educate patients and prescribers on the appropriate (safe, effective, and cost-effective) use of prescribed and over-the-counter medicines.(117) There has been abundant QUM activities undertaken across the country, thus a geographical Mapping Project (QUMmap) was developed in 1999 to assist coordination of QUM research and seeding projects.(118) QUM projects are collated and searchable via a web-based interactive QUMmap database thus providing a valuable tool for policy planning and implementation of QUM initiatives. In addition, the National Prescribing Service (NPS), funded by the federal government, was established in 1998 as an independent, national service arm for QUM. Through its programs and consistent

delivery of balanced information, primarily to general practitioners, community pharmacists and consumers, the NPS has vigorously supported quality prescribing and use of medicines to date.(115, 119)

1.5.3.1 Prescribing budgets

An approach to restricting expenditure on medicines is to set a financial limit on prescribing, such that above this limit the cost of any prescription medicine is paid for out of the budget allocated for physician remuneration. This method to reduce inefficient drug prescribing has been used in several countries.(120, 121) For example, in Germany, a prescribing budget cap had controlled drug expenditure markedly since it was introduced in 1993.(122, 123) However, restricting budgets does not necessarily enforce quality prescribing and can lead to the under use of drugs, thus savings in drug expenditure may be off-set by increases in expenditure on other areas such as specialists and hospital care.(121, 124) A capitation on prescribing has also been used in general practice in the UK. Harris and colleagues (125) found that the absolute cost of prescribing increased by 66% in non-fundholders and by 56-59% in fundholders between 1990 and 1996. This was achieved by a reduction in the average cost per item prescribed rather than by decreasing the number of items prescribed.(125) Overall, evidence of poorer treatment by fundholders compared to non-fundholders has not been found.(126)

1.5.3.2 Prescribing guidelines

National medical guidelines for doctors with respect to diagnosis and treatments are used in countries such as Australia, the UK, France and Germany. As an incentive for following these guidelines, doctors are awarded an increase in their fees in some

countries (e.g. France and Germany), while those who fail markedly to comply with the guidelines face fines.(120) In the UK, national evidence-based prescribing guidance on the use of a particular medicine under the National Health Service is provided through National Institute for Health and Clinical Excellence (NICE, formerly known as the National Institute for Clinical Excellence). Findings from a regional study (based on data collected via survey, interviews, and prescribing analysis) were suggestive that NICE guidance alone had little impact on prescribing by general practitioners.(127) Commissioned by NICE, a study by Sheldon et al (128) used multiple methods (interrupted time series analysis, review of case notes, survey and interviews) to examine the pattern of implementation of NICE guidance.(128) Sheldon and colleagues found some changes in clinical practice in line with NICE guidance, for example, prescribing of taxanes and orlistat had increased significantly since relevant NICE guidance was published. However, implementation of NICE guidance was variable, particularly influenced by professional opinion and the availability of funding locally.(128)

A number of information resources to improve the quality of prescribing and use of medicines have been produced in Australia. These include: the "Australian Medicines Handbook" that covers all medicines marketed in Australia together with useful information about prescribing under the PBS; a national independent journal of therapeutics ("Australian Prescriber"), and a series of clinical guidelines ("Therapeutics Guidelines").(115, 117) These are also readily accessible online. The NPS also acts as a source of objective information through its newsletters. A survey found that the newsletters were well-regarded and helpful for prescribing practice and therapeutic choices in about 60% of general practitioners and pharmacists.(129)

1.5.3.3 Information and feedback

Information feedback systems for physicians are available in several countries, such as France, Germany, New Zealand, the Netherlands, the UK,(120) and Australia, the aim being to enhancing effectiveness of prescribing. In the UK, data on prescribing analysis and cost (prescribing analysis and cost tabulation, PACT) are provided to general practitioners on a quarterly basis to enable doctors to monitor their own prescribing patterns.(130) The National Prescribing Centre in the UK was established in 1996 (http://www.npc.co.uk/index.htm). The role of this health service organisation, similar to that of the NPS in Australia, is to promote and support quality, cost-effective prescribing and medicines management to help improve patient care across the National Health Service in the UK.

In Australia, through the NPS, a prescriber feedback program for selected PBS medicines is in place together with other interventions such as newsletters, prescription analysis and feedback, clinical audit, and educational visiting.(119) This program has been evaluated using time-series analyses for changes in drug utilisation and qualitative methods. About 90% of general practitioners and 9% of pharmacists across the country had participated in one of these programs over the five-year implementation.(129) Further, the NPS has implemented several educational programs (covering topics such as antibiotics in primary care, management of dyslipidaemia, management of hypertension, use of cyclo-oxygenase-2 inhibitors, and management of dyspepsia). As a result of changes in prescribing practices through these educational programs, the NPS programs have generated PBS cost savings.(129) Additional programs for the community and consumers are being coordinated.(119) Similarly, a program in support of QUM, known as the Veterans' Medicines Advice and Therapeutics Education Services

(Veterans' MATES), was recently introduced by the Commonwealth Department of Veterans' Affairs. This program aims to improve the use of medicines in the veteran community.(131) Data on patterns of dispensing and service delivery are used to identify areas of medication misadventure. Patient-based feedback is provided, primarily for the veterans and their general practitioners and community pharmacists, to assist in improving the management of their medicines.(132) Clinical modules are also produced as a result of this program several times a year, each focusing on a particular aspect of medicines management (for example, use of adjunctive medicines in diabetes and use of beta-blockers in congestive heart failure).(131) A survey study of general practitioners and veterans found on average a high degree of satisfaction (more than 75%) with such feedback and therapeutic information, and that prescribers were likely to review their patients as influenced by recommendations in the clinical modules.(132)

1.5.3.4 *"Authority-required" prescribing (Prior-authorisation)*

"Authority-required" prescribing (also termed "prior-authorisation" in the USA) is an approach to drug cost containment. It is used in several developed countries, including Australia, to restrict the use of specific medications by requiring the prescriber to get an advance approval by the reimbursement agency for the drug before prescribing to qualify for reimbursement. New and expensive medicines, medicines that have a potential of inappropriate use, and effective drugs for which there are cheaper therapeutic equivalents typically are authority-required benefits. A major purpose of authority-required prescribing is to allow patient access to essential pharmacotherapies while promoting cost-effective prescription drug use.(133) In Australia, "authority required" restrictions under the PBS are evidence-based (on the basis of both clinical and economic evidence) and regulate the use of

such medicines to the area where the evidence supports their use.(134) Authority-required prescribing often requires: (i) the submission of a patient's clinical information for review,(135) and (ii) step therapy that requires patients to try low-cost medicines before a more expensive treatment on authority is approved for use and reimbursed. A critical review by MacKinnon and colleagues revealed that authority-required prescribing appears to be effective in reducing drug-related costs.(133) However, rigorously designed studies are needed to evaluate the effects of authority-required prescribing on clinical and humanistic (such as health-related quality of life and patient satisfaction) outcomes.(133) There is some evidence suggesting that prior-authorisation is effective in reducing costs of medicines while encouraging use of cheaper alternatives without evidence of adverse medical consequences.(136) A survey in Australia found that doctors showed an appreciation of "authority-required" prescribing as a regulatory system to provide most medicines to the most people at the least cost. However, doctors placed greater emphasis on clinical and patient considerations over authority-required prescribing criteria in making prescribing decisions.(137) Attention has recently been given by the Australia government to reduce bureaucracy and streamline "authority-required" processes, for example, requests for 'authority' are now possible online.(138)

1.5.4 Interventions for influencing patient demand

1.5.4.1 *Patient co-payment*

The approach of increasing financial responsibility by patients is often used to reduce the demand for drugs and provide an incentive for patients to reduce their consumption of drugs. Patient cost-sharing requires patients to share the costs of medicines with the aim to discourage the use of unnecessary medicines thereby

containing increasing pharmaceutical expenditure. Cost-sharing can be defined in several ways: (i) a proportion of the total price; (ii) a fixed charge per prescription; (iii) an annual deductible; and (iv) any combination of these. Many countries use a co-payment proportional to the drug price. The proportion of cost-sharing differs across countries: 10% in Switzerland, 50% in Norway, and co-payments are set to 40% of the sale price in Spain with a maximum annual charge. Germany, the Netherlands, the UK, and Australia have largely opted for a fixed co-payment system. In Sweden and New Zealand, there is a fixed maximum prescription charge plus a premium for drugs costing more than the reference price.(139) Both Finland and Italy have systems of differential cost sharing. A prescription charge plus a percentage of the price depending on the class of drug is the approach in Italy;(95) and in Finland, there are three categories of reimbursement with different levels of co-payments and deductibles. In the USA, a multi-tiered co-payment system is used by managed care organisations, patient contributions are often based on drug acquisition cost.(140)

Co-payments have been shown to reduce the use of drugs and prescription drug expenditure in the USA.(141, 142) For example, a study of a multi-tier pharmacy program in the USA showed that higher co-payments for medicines promoted some patients to discontinue use of a medicine, rather than switch to a less expensive drug.(143) Patient cost-sharing strategies have raised concerns among healthcare providers and consumers regarding reduced adherence to ongoing care and restricted access to new treatments.(144, 145) Increasing prescription charges in the UK were found to be associated with a significant reduction in the use of prescribed drugs by patients.(146) In Canada, there is also some evidence that increases in co-payments have restricted access to medicines, resulting in undesired effects (such as reductions in use of essential drugs and a higher rate of emergency department visits associated with these reductions) among the poor and elderly.(147, 148) A

qualitative study found that patients were generally cost-conscious, and may use various strategies to reduce the spending on medicines, such as by not having some prescribed items dispensed, taking a smaller dose or buying a cheaper over-the-counter product.(149) A recent systematic review of the international literature on the effects of drug cost-sharing also supported the view that co-payments decrease the use of prescription drugs by the poor and those with chronic conditions.(150) Reflecting the findings of international studies, research in Australia has also shown that prescription utilisation decreases with increased patient out-of-pocket costs. Medicines classified as 'discretionary', that is, used for symptom relief were considerably affected by changes of patient co-payments.(151) Survey studies have found that in approximately 20% of patients, patient co-payments influenced when and how they access and use prescription medicines in Australia.(152, 153) As the burden of direct co-payment falls more heavily on the less privileged groups of the population, many countries (including Australia) have implemented specific safety nets to counter the potential negative effects of co-payments.(70)

In addition to the use of patient co-payments, the Australian government also launched a campaign "Pharmaceutical Benefits Scheme Community Awareness" in 2003 noting that the cost of the PBS is increasingly rapidly and the whole scheme may eventually become unsustainable. Unfortunately, this campaign was more reflective of government concern about unnecessary use rather than patient education. Doran and Henry (154) commented that by focusing on patient behaviour and 'waste', the government had lost an opportunity to initiate a balanced and constructive debate about the future viability of the PBS.(154) Research by Doran and colleagues (155) explored patients' perspectives about medicine use to examine whether 'unnecessary' utilisation of medicines ('moral hazard') was observed in practice. This qualitative study found that patients did not appear to be

taking advantage of affordable access to prescription medicines and that necessity, typically established by the prescribing doctor, was the principal influence on patients' decision on using a prescription medicine.(155)

1.5.4.2 Prescription drug benefit caps

A cost containment strategy used in the USA is to limit the number of drugs that may be reimbursed or the prescription coverage in a specified period.(120) Patients are required to pay the full price of drugs consumed after their spending exceeds the 'cap' amount. Quasi-experimental studies by Soumerai and colleagues (156-158) reported that patient caps reduced the number of prescriptions filled more significantly than a prior co-payment system. These studies also revealed a substantial reduction in the use of essential drugs such as insulin and diuretics, and an increase in related healthcare costs such as medical services and institutionalisation in nursing homes.(156-158) Using survey techniques, Tseng and colleagues reported that Medicare beneficiaries who reached the annual cap on drug benefits had experienced difficulty paying for prescription medicines and a decreased use of needed medicines in this population.(159) A recent study found an association between drug benefits cap and reduced drug consumption (poorer adherence to drug therapy) and unfavourable clinical outcomes.(160) Thus the savings in drug costs by capping may be offset by increases in the costs of hospitalisation and emergency department care.

1.6 Quality of care, costs, and ethics

Prescription medicines have an increasingly important role in healthcare. As described in the previous section, drug cost-containment policies can help to control rising pharmaceutical expenditure. However, beyond drug acquisition cost, these policies affect prescribing and patients' access to medicines. Patients' health may be compromised if they do not have adequate access to drug therapy and may result in compensatory increases in expenditure on other healthcare resources such as hospital spending ("cost-shifting"). A cost-containment policy is likely to have little impact on quality or outcomes of care if it can selectively reduce the use of unneeded medications while preserving essential care ("intended effects"). However, unfortunately such policies are likely to reduce necessary as well as unnecessary care when implemented ("unintended effects").(121) Therefore, the impact of cost-containment policies on quality of care and economic implications requires rigorous research.(121) The ethics of restrictions on access to medicines also need to be carefully considered and reviewed.(62, 121, 161) The challenge faced by many health systems is to deal with rising drug expenditure while not denying or limiting access to those drugs that improve therapeutic outcomes and health-related quality of life. This challenge is likely to be increasingly difficult as pharmaceutical expenditure is likely to continue to rise. Evaluation of administrative policies and programs in pharmaceutical benefit management is inadequate.(133, 162) The significance of evaluation is well described by Ratanawijitrasin (163): "to ignore evaluation and to implement policy intervention based on logic and theory, is to expose society to untried and untested measures in the same way that patients were exposed to untested medicines". It is crucial that governments and researchers increasing their efforts to identify the most appropriate approach that reduces the conflict between the goals of economic efficiency (namely to maximise the output, in terms of improved health, from the resources available) and equity of access to healthcare services and medicines.

1.7 Challenges posed by biopharmaceuticals

In the context of limited healthcare resources, new technologies may often be seen as a cause of budgetary difficulty and are assessed with increasing scepticism. The recent availability of biotechnology pharmaceutical products has highlighted this dilemma. Biopharmaceuticals – recombinant therapeutic proteins, monoclonal antibody-based products used for medical purposes, and nucleic acid-based medicinal products – represent about 25% of new pharmaceuticals coming on the market.(164) They represent a relatively new area of prescription medicines. The growth in successful biopharmaceutical development resulted from a combination of factors, such as accumulating information from the human genome project, genomics and proteomics, technological developments in molecular biology, better scientific understanding of drug targets, and increased experience with this class of pharmaceuticals by drug developers and regulators.(165) There is a continued emphasis on development of biopharmaceuticals for serious or life-threatening diseases and a growing focus on chronic conditions such as rheumatoid arthritis. Major target conditions include cancer, infectious diseases, autoimmune disorders, cardiovascular disease, and diabetes.(164) Many of these biopharmaceutical medicines provide highly sophisticated treatment for rare or chronic conditions (Table 1.3), such as non-Hodgkin's lymphoma, for which there previously were no viable pharmaceutical options.

Table 1.3 Examples of biopharmaceuticals

Drug name	Primary use	Year approved by the US Food and Drug Administration
Rituximab	Non-Hodgkin's lymphoma	1997
Trastuzumab	Breast cancer	1998
Etanercept	Rheumatoid arthritis	1998
Infliximab	Crohn's disease	1998
	Rheumatoid arthritis	1999
Anakinra	Rheumatoid arthritis	2001
Imatinib	Chronic myeloid leukaemia	2001
Adalimumab	Rheumatoid arthritis	2002
Gefitinib	Non-small cell lung cancer	2003

1.7.1 Uncertainties around pricing of and access to biopharmaceuticals

Biopharmaceuticals pose numerous challenges for healthcare systems and payers, although the issues around economic assessment of products in this novel area of medical intervention are mostly the same as for other pharmaceuticals.(166-168) Pricing and reimbursement decisions are usually made when a product is launched. The major difficulty facing decision makers who assess cost-effectiveness of medicines in general is the uncertainty around long-term outcomes due to: (i) the artificial nature of clinical trials (e.g. small sample sizes, and short period of follow-up), (ii) uncertainty about the assumptions and parameters used in economic evaluations, and (iii) in the case of biopharmaceuticals, the high level of innovation since biopharmaceuticals often fill major gaps in therapy, that is, there is no ready comparator in that therapeutic class, and a judgment must be made on the acceptable cost per unit of health outcome; this implies greater uncertainties.(166, 167) While clinical trials demonstrate clinical efficacy, they usually do not demonstrate longer term, broader health outcomes and resource implications. In order to estimate the QALYs gained by therapy, it is necessary to track benefits for a patient over the long-term. Economic evaluations take into account disease severity

at the time of intervention, but also predict severity in future years in the case of non-intervention. Projection of benefit beyond the period of the trial is one important and challenging issue for economic analysis. Reimbursement decisions are often made on the basis of inadequate data on the effectiveness of medicines because clinical trial data are generated prior to marketing of new medicines and primarily to support regulatory goals of acceptable quality, safety and efficacy. These regulatory goals are very different to those expected within the reimbursement process, which increasingly relies upon comparative cost-effectiveness. Promising developments may be curtailed because of their unfavourable cost-effectiveness in early stages of development.(166) Therefore, information relevant for future reimbursement should be incorporated as early as possible in drug development.(169)

There are also safety concerns. Protein products for human use may induce an immunogenic response which impacts their safety profile. "Humanisation" of biopharmaceuticals may minimise, but not eliminate completely, the problem of immunogenicity.(165) It has been proposed that governments have an important role and need to be proactive to (i) ensure that meaningful clinical and economic data are generated in the product research phase, and (ii) manage the introduction and wider use of the medicine in the community with further evaluation and surveillance.(167) Given that reimbursement decisions are taken under uncertainty of longer term outcomes, an approach adopted by other agencies, such as NICE in the UK and the European Agency for the Evaluation of Medicinal Products, is to make decisions conditional on the generation of additional post-marketing evidence of safety and efficacy.(170) This approach is gaining support in the USA for mandated studies to confirm the drug's efficacy and safety by its national regulatory authority, the Food and Drug Administration.(171, 172)

Real-world trials may provide useful answer to questions relevant to health policy and reimbursement, and provide evidence on the effectiveness and cost-effectiveness of the product in practice. Although a prospective, randomised trial designed primarily to obtain information on cost-effectiveness and to assist treatment decisions under actual practice would be ideal, consensus on specific design features of such a trial has not been reached. A real-world trial of inhaled insulin (Exubera®) is currently underway that examines rates of uptake (acceptability), and the clinical and economic outcomes of introduction of inhaled insulin into practice (e.g. glycaemic control and resource use).(173) More trials of this type are likely and warranted.

1.7.2 The high cost of biopharmaceuticals

The higher costs for biopharmaceuticals may arise, in part, from more complex manufacturing processes, royalties to owners of patents, the desire of manufacturers to recoup the costs of research and development and to realise profits, and the lack of equally effective therapeutic competition. Further, a majority of these drugs are administered by injection or infusion, or they are aerosolized products and thus often require special handling or administration, or both.(174) Price setting for biopharmaceuticals is problematic, particularly when the existing therapies that serve as a comparison are traditional chemical entities of relatively cheaper cost.(166, 167) Relatively higher costs of biopharmaceuticals are likely to generate ethical considerations such as resource issues.(175) Careful economic analysis is important because a high price does not necessarily imply good value for money nor guarantee greater efficacy.(166) Besides reimbursement and controls on access, some further important issues that healthcare systems and payers need to

manage include clinical protocols, specialised drug delivery and handling, patient education, drug administration, treatment oversight, and data management.(174) In addition, because there is uncertainty regarding the longer term efficacy and safety of biopharmaceuticals, healthcare systems and payers will need to work collaboratively with other stakeholders to ensure long-term data are collected through phase IV clinical trials, and pharmacovigilance and post-marketing studies.

1.7.3 Access to biopharmaceuticals

In some circumstances when the highly specialised medicines are not considered of acceptable cost-effectiveness for subsidy, different strategies may be established by funding bodies to make them available and affordable, often under the pressure of healthcare professionals, patients, the public, as well as the pharmaceutical industry. For example, interferon beta and glatiramer acetate for the treatment of multiple sclerosis were not considered by NICE to be cost-effective for wide use, and were not subsidised by the National Health Service in the UK.(176) Subsequently, a risk-sharing scheme was established by the Department of Health and the manufacturers to fund interferon beta and glatiramer and to assess the real life cost-effectiveness of these drugs.(177) Subsidised treatment is being provided to a subset of patients (about 15%) with multiple sclerosis and their health outcomes are being monitored over 10 years. The scheme has been criticised for its scientific flaws and practical problems such as the lack of a randomised comparison group.(178) Nevertheless, this arrangement is a compromise to make the treatments available by sharing the financial burden with industry and represents an attempt to deal with the uncertainties about cost-effectiveness of treatments.(179)

1.8 Summary

This chapter has provided an outline of the components of a national medicines policy that are essential for achieving appropriate access to medicines, as recommended by the WHO (Section 1.2). In light of growing pharmaceutical expenditure (Section 1.3), setting "limits" (priority setting) and use of methods to control drug expenditure are inevitable (Sections 1.4 & 1.5). However, there is a critical need to examine the outcomes of these strategies that potentially impede access to needed, effective medicines. Clearly, three major areas in such an evaluation would include clinical, economic, and ethical outcomes (Section 1.6).

There is a paucity of literature relating to evaluation of access to highly specialised but expensive medicines, particularly at a national level. Managing the access to these drugs will be increasingly challenging as the clinical uses of existing biopharmaceuticals expand, and new biopharmaceuticals emerge for treatment of a greater number of medical conditions. Due to uncertainties and the considerable higher costs, the challenge lies in how to best manage access to these drugs in a manner that is affordable, equitable, feasible, and most importantly, enables rational use of these drugs. Adoption of expensive drugs into routine clinical practice is likely to be influenced by clinical advantages, economic concerns, and payment policy issues.(180) How to develop arrangements for access to these drugs and evaluation of access is a research priority. The present research has aimed to redress this critical gap. Careful examination of the recent developments in targeting access to highly specialised, expensive medicines in Australia contributes to the knowledge and understanding of managing access to expensive medicines under drug reimbursement systems.

2. ACCESS TO HIGH-COST BIOLOGICAL MEDICINES IN AUSTRALIA

In this chapter, a brief overview of various mechanisms of access to medicines in Australia is presented, followed by a background to the evolving system of restriction on access to high cost medicines under Australia's national subsidy system – the Pharmaceutical Benefits Scheme. The controlled access scheme for biological anti-rheumatic drugs, a representative example, is described in detail. An overview of Australia's National Medicines Policy – the context in which access to high cost drugs occurs – is discussed as it is critical to understanding the relevance this framework has in current and future approaches to accessing high cost medicines. The broad hypothesis that was tested in this thesis is introduced and an outline of the domains of investigation and methodologies employed is presented.

2.1 Introduction: Access to medicines in Australia

The Australian healthcare system is based on the fundamental principle that residents should have equitable access to needed, effective and safe healthcare, regardless of their ability to pay.(181) Australia is a federation compromising a national government (the Commonwealth Government), and eight state and territory governments. Availability of prescription medicines in Australia is a "two-stage" process that distinguishes between access and subsidised-access to approved medicines, these stages being: (i) application for registration to gain licensing approval, and (ii) application for subsidisation of the cost of the medicine.

2.2 Registration of Medicines

Under the *Therapeutic Goods Act 1989,* before a medicine is available for use in Australia it must be approved by the regulatory authority, the Therapeutic Goods Administration (TGA) of the Commonwealth Department of Health and Ageing. The medicine is evaluated on the basis of its safety, efficacy and quality by the TGA. Independent advice on applications for registration of prescription medicines is provided to the TGA by the Australian Drug Evaluation Committee (ADEC). Advice is then given to the Australian government regarding whether the drug should be registered. After registration, the medicine may be marketed and prescribed (but not automatically subsidised) for the approved indications.(182, 183)

2.3 Subsidy of Medicines

2.3.1 The Pharmaceutical Benefits Scheme (PBS)

The Pharmaceutical Benefits Scheme (PBS) was established in the 1950s with 139 medicines considered to be necessary provided free of charge.(184) The PBS is funded by the Commonwealth Government and governed by the Australian *National Health Act 1953* and the *National Health (Pharmaceutical Benefits) Regulations 1960*. The PBS is the major mechanism that supports universal access to a wide range of prescription medicines. The principal goal is to provide medicines that are of acceptable quality, safety and efficacy in an effective and equitable manner, at a cost that individuals and the community can afford (http://www.health.gov.au/pbs/).(185)

Once a medicine is registered, the pharmaceutical company can apply for subsidy by the PBS ("PBS listing") for the indication(s) approved by the TGA. The process of achieving subsidy for a drug is illustrated in Figure 2.1. The sponsor is required to provide data comparing the drug with the best available comparator (comparison of the safety and efficacy of the new agent with existing therapy that is likely to be replaced in practice), an economic evaluation of the increase in benefits and costs, as well as a financial analysis from the perspective of the PBS and the health budgets. Australia was the first country to introduce a mandatory requirement for economic analysis to select pharmaceuticals for subsidy in 1993.(106, 186)
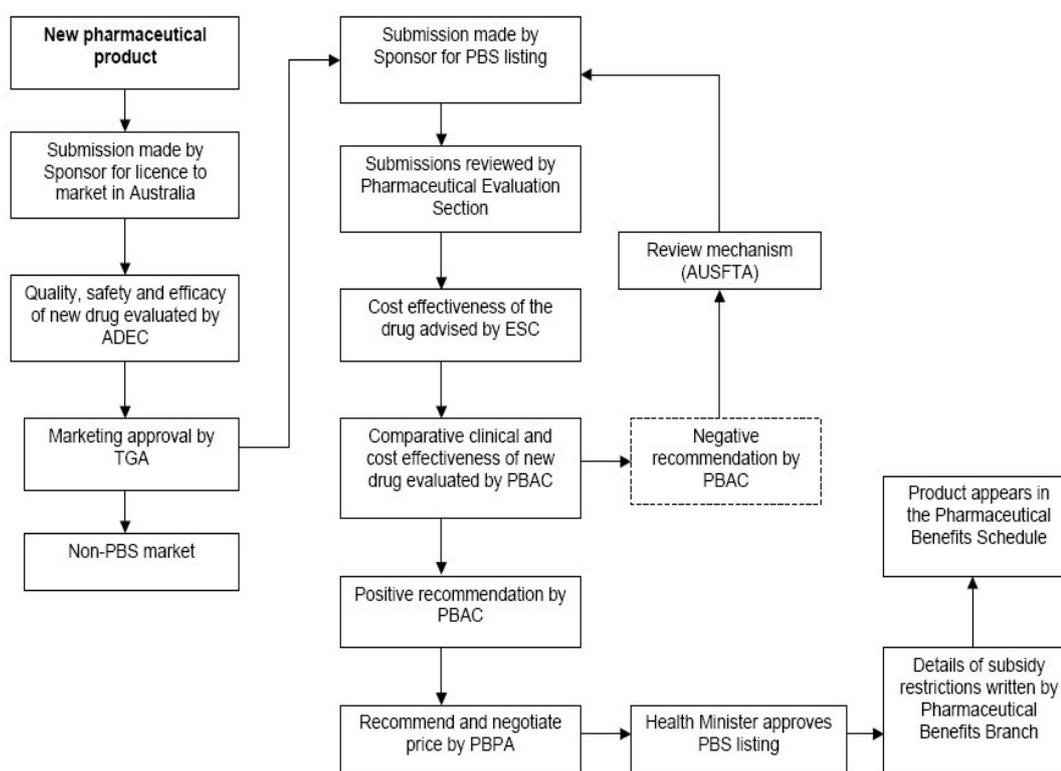
Figure 2.1 Process of drug subsidy under the Pharmaceutical Benefits Scheme

ADEC= Australian Drug Evaluation Committee; AUSFTA= Australia-United States Free Trade Agreement; ESC= Economic Sub-committee; PBAC= Pharmaceutical Benefits Advisory Committee; PBPA= Pharmaceutical Benefits Pricing Authority; PBS= Pharmaceutical Benefits Scheme; TGA= Therapeutic Goods Administration

With regard to the process, submissions for PBS subsidy are first assessed by the Pharmaceutical Evaluation Section (PES), which evaluates the accuracy and validity of the data presented (including the literature, statistics and data analyses) and provides summaries of the information and reports any uncertainties to the Pharmaceutical Benefits Advisory Committee (PBAC) (Figure 2.1). The PBAC is an independent statutory body established under the *National Health Act 1953*. Its membership includes clinical pharmacologists, specialist physicians, general practitioners, health economists, and consumers who advise the Federal Minister for Health about which medicines should be subsidised by the PBS. In making its recommendation (positive or negative), the PBAC assesses and considers the effectiveness, cost-effectiveness, and the clinical place of the new pharmaceutical product compared to alternate therapies from a societal perspective. The types of economic evaluations considered by the PBAC are summarised in Table 2.1.(187) The PBAC may specify the appropriate uses, quantities and maximum number of repeat prescriptions to which the subsidy should apply.

Table 2.1 Types of economic evaluations considered by the PBAC

Cost-effective analysis	An economic evaluation that compares therapy involving the proposed drug with therapy involving its main comparator(s) having common clinical outcome(s) in which costs are measured in monetary terms and outcomes are measured in natural units.
Cost-utility analysis	An economic evaluation that compares therapy involving the proposed drug with therapy involving its main comparator(s) in which costs are measured in monetary terms and outcomes are measured in terms of extension of life and the utility value of that extension (e.g. quality-adjusted life-years or health-year equivalents).
Cost-benefit analysis	An economic evaluation compares therapy involving the proposed drug with therapy involving its main comparator(s) in which both costs and benefits are measured in monetary terms to compute a net monetary gain/loss or benefit gain/loss.
Cost-minimisation analysis	An economic evaluation that finds the least costly alternative therapy after the proposed drug has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and toxicity.

Source: Glossary for preparation of PBAC submissions (http://www.health.gov.au/)

There are two sub-committees that provide advice to the PBAC during the process: (i) the Economic Sub-Committee (ESC) reviews the economic evaluations conducted by the PES and advises the PBAC about both the clinical and cost effectiveness of the new medicine as well as any issues that have been raised by the evaluations. Its membership includes clinicians with expertise in clinical epidemiology and/or health economics; and (ii) the Drug Utilisation Sub-Committee (DUSC) advises the PBAC on patterns and changes of drug use associated with subsidy restrictions.(85) Once a product is recommended for subsidisation by the PBAC, the Pharmaceutical Benefits Pricing Authority (PBPA) negotiates price with pharmaceutical suppliers (Figure 2.1). In order to secure a reliable supply of pharmaceutical benefits at the most reasonable cost to Australian taxpayers and consumers, the PBPA is responsible for recommending prices for new products as well as reviewing prices of PBS-subsidised products.

In 2004, the PBS covered 650 drugs, available in a total of 1,600 forms and strengths (items), marketed as nearly 2,500 different drug products (brands). Medicines subsidised under the PBS may be prescribed as either unrestricted, restricted (for specific therapeutic uses), or as 'authority required' (requiring prior telephone or written approval from Medicare Australia, previously the 'Health Insurance Commission', a government body that administers the PBS and other health programs nation-wide). Restrictions apply to 844 of the items, and 351 are 'authority required' prescription medicines.(188) In 2004/05, the total cost of the PBS was over A$6 billion and government expenditure amounted to 84% (A$5.3 billion) of this total cost.(189) All Australians have access to medications through the PBS. Under Section 85 of the *National Health Act 1953*, consumers are required to make a fixed, statutory co-payment for subsidised medicines. As of January 2006, general patients contribute A$29.50 per prescription and concessional patients A$4.70. Concessional patients are those who hold any one of the following: a Pensioner Concession Card, a Commonwealth Seniors Health Card, a Health Care Card (from Social Security), Repatriation Health Card, a Safety Net Concession Card or a Safety Net Entitlement Card. The PBS funds the difference between patient co-payment and the cost of medicines irrespective of that cost. The cost of medicines is subsidised through the Repatriation Pharmaceutical Benefits Scheme (RPBS) for veterans and eligible dependants.

2.3.1.1 Section 100 of the National Health Act 1953

The Highly Specialised Drugs Program of the PBS funds a range of specialised, expensive medicines that are supplied through public and private hospitals using specialist facilities.(190) This program is administered by the Pharmaceutical

Access and Quality Branch of the Commonwealth Department of Health and Ageing. Medicines funded under this program are highly targeted agents typically subsidised for precisely defined sub-sets of patients with registered indications for which cost-effectiveness and safety have been demonstrated. These medicines usually have a "high unit cost" ("high unit cost" is defined by the Commonwealth Department of Health and Ageing as "a cost beyond the normal financial capacity of individuals and imposing significant financial burden on specialised institutions").(94) Typically, these medicines are subsidised for sub-sets of patients with serious conditions such as cancer, human immunodeficiency virus/acquired immunodeficiency syndrome and organ transplantation. In 2004/05, there were 65 medicines subsidised under this program. Total expenditure for the program was A$468.8 million, a 16.5% increase over the previous year.(191)

Section 100 also allows for special access where pharmaceutical benefits cannot be conveniently supplied. Patients of Aboriginal and Torres Strait Islander health services (these are either Aboriginal community controlled health services or state and territory operated services) can receive medicines directly from the services at the point of consultation, an innovative program established in late 1990s.(192)

2.3.2 Hospitals

There is a mix of private and public provision and funding in the hospital sector in Australia.(193) In 2001/02, expenditure on the use of pharmaceuticals in hospitals was A$1,105 million for public hospitals and A$210 million for private hospitals (Figure 2.2).(194) Medicines in private hospitals are funded by the PBS, third-party payers (e.g. private health insurance) for non-PBS medicines, as well as by out-of-pocket expenditure by individuals.(195) In public hospitals, there is no direct cost of

medicines to persons who are inpatients. Medicines are primarily funded by the hospital under the Medicare Agreements between the States and Territories and the Commonwealth Governments.(181) Decisions on budgetary allocation (capped funding) are made at a number of levels. These include the State Health Department, health district or area health services and the individual hospitals.(195) In 2002/03, five percent of the total hospital expenditure in public hospitals was on medicines.(196) Costs of medicines for outpatients, discharge and day patients have been met by the PBS in certain participating public hospitals since the 1998-2003 Australian Health Care Agreement.(197) Costs of inpatient medicines still remains the responsibility of the hospital.
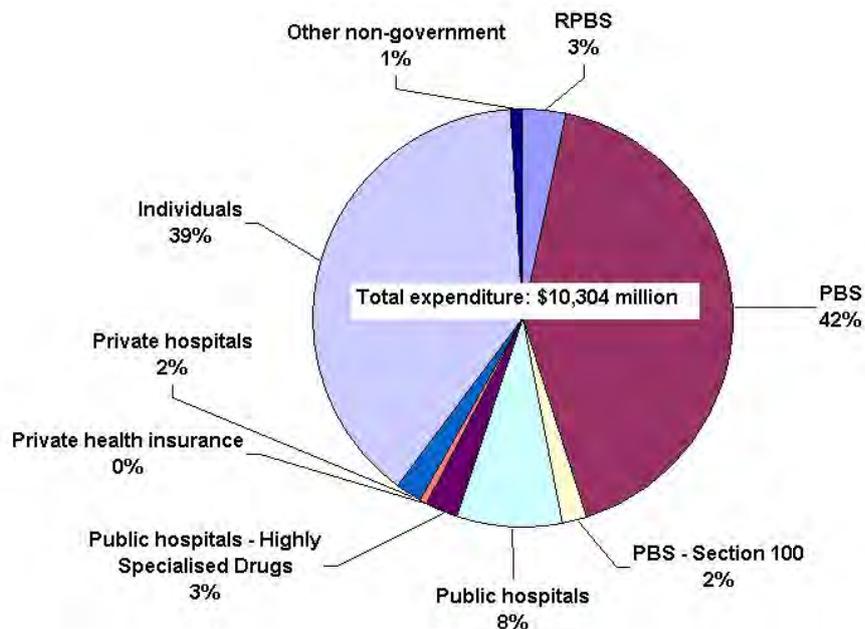
Figure 2.2 Expenditure on pharmaceuticals in Australia 2001-2002 (194)

Note: 'Pharmaceuticals' include prescribed medicines (both PBS and non-PBS subsidised), over-the-counter medicines and other non-durable therapeutics (single use or limited re-usage items) – as defined by Australian Institute of Health and Welfare.
PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme

2.3.3 Other Mechanisms of Access

Patients may pay the full cost of the medicine via a private prescription, or through a limited number of alternative schemes that supply medicines outside the PBS. These include, the 'Orphan Drug Program', the 'Lifesaving Medicines' program, the 'Special Access Scheme', Clinical Trial Schemes, and Importation for personal use. Mechanisms of access to medicines in Australia are summarised in Table 2.2.

Table 2.2 Categories of government funded access to prescription medicines in Australia

Commonwealth government, PBS	Unrestricted benefits	No restrictions on therapeutic uses
	Restricted benefit drugs	Restricted for specific therapeutic uses; these do not require prior approval from Medicare Australia
	Authority required drugs	Require prior approval from Medicare Australia or from the Department of Veterans' Affairs
	Section 100 ("Highly Specialised Drugs Program")	Allows access to highly specialised drugs, including chemotherapy drugs, by targeted patient groups who meet strict clinical criteria
Commonwealth government, TGA	Orphan Drug Program	Allows access to drugs that are accepted as clinically effective in treating rare diseases
	Special Access Scheme	Provides for the import and/or supply of an unapproved therapeutic good for a single patient, on a case-by-case basis, if approved by the TGA
State governments	Public Hospitals	Restricting drug supplies to discharged patients (supplies often cover only 2-3 days of treatment)

PBS= Pharmaceutical Benefits Scheme; TGA= Therapeutic Goods Administration

2.3.3.1 Orphan Drug Program

Orphan drugs are used to treat, prevent or diagnose rare diseases that affect approximately 2,000 individuals per year in Australia. The Orphan Drug Program encourages pharmaceutical sponsors to market these drugs by reducing registration and other costs and facilitating shorter TGA approval times. This is because these drugs are likely to have a low gross financial return, such that registration would be unlikely to occur without assistance.(198)

2.3.3.2 Lifesaving Medicines

The Commonwealth Government funds supply of certain expensive and lifesaving medicines that are clinically effective but not cost-effective as evaluated by the PBAC. For example, imiglucerase (Cerezyme®) for the treatment of Gaucher's disease is supported under this scheme. Funding for this program is limited and reviewed yearly. Access to these medicines is subject to certain conditions agreed to by the Ministers for Health and Finance and under specified eligibility criteria.(198)

2.3.3.3 Unapproved Medicines

Medicines that are unapproved in Australia (i.e. not registered by the TGA) are potentially accessible. The Special Access Scheme funds drugs not yet approved for the Australian market for treatment of individual patients with serious medical conditions after approval by the Drug Safety Evaluation Branch of the TGA.(199) Access to unapproved drugs is also possible through participation in clinical trials, either under the Clinical Trial Exemption Scheme (CTX) which requires data to be assessed by the TGA prior to approval, or under the Clinical Trial Notification Scheme (CTN) through which institutional ethics committees are responsible for

approval of the trial. Individuals are allowed, under strict criteria, to import most therapeutic goods (including alternative medicines) for personal use under the Personal Import Scheme.(198, 200)

2.4 A need for different models of access to 'high cost' medicines in the community

The operation of the PBS dominates the prescription drug market in Australia.(189, 201) This system has attracted considerable attention worldwide as Australian pharmaceutical prices are markedly lower than those in other countries with comparable living standards.(71) The monopolistic bargaining power of the Australian government in negotiating drug prices,(202) and the use of reference pricing have contributed to the lower drug prices.(71, 203) However, innovative pharmaceutical products are purchased by the government at prices comparable to other countries.(71)

The fiscal sustainability of the PBS has been under intense scrutiny by federal health and financial public policy makers in recent years.(204) The cost of the PBS over the last decade has been increasing at an annual rate of between 8 and 20%,(85) a rate that is deemed by many to be economically and politically unsustainable. Growth in government expenditure on pharmaceuticals averaged 10.8% per annum between 1994/95 and 2004/05.(205) While the growth rate of government outlays on pharmaceuticals has slowed in the last year (5.8% increase in 2004/05),(189) government expenditure on medicines has increased at a rate greater than other areas of health care (accounting for 25% of total growth in health expenditure in 2002/03).(206) In part, this disproportionate expenditure reflects the

cost of the continued introduction of new, but increasingly expensive, medicines including the new biotechnology-derived drugs.

Pressure on the PBS was intensified in 2000/01 because of a dramatic, unanticipated increase in its expenditure (a 19% increase over the previous year). This 'blow-out' resulted from listing costly new medicines and substantial under-estimates of prescribing rates for a very few medicines, notably omeprazole, celecoxib, and rofecoxib.(207-209) It is known that prescribing beyond the PBS restrictions (termed 'leakage') for cyclo-oxygenase-2 inhibitors was the major cause of the cost 'over run', although it is difficult to determine the level of leakage (Figure 2.3).(207, 209)
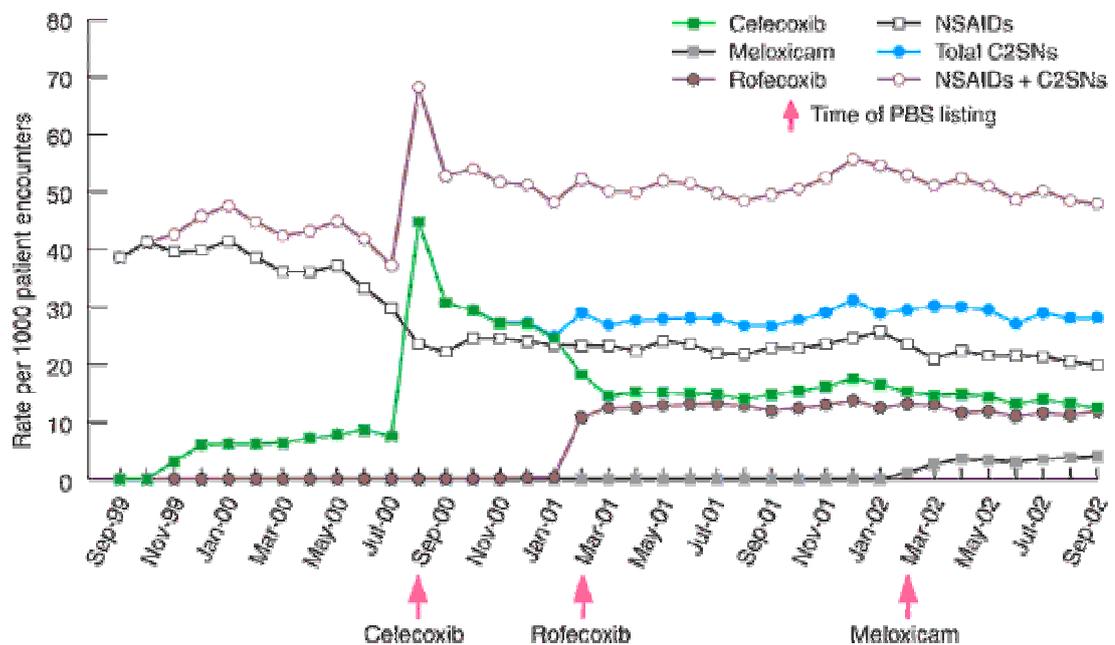
Figure 2.3 PBS prescription rate per 1000 patient encounters of cyclo-oxygenase-2 inhibitors and non-steroidal anti-inflammatory drugs (Source: Kerr et al, Med J Aust 2003; 179: 403-407) (207)

The PBS, similar to other payers in public and private health systems, faces challenges of increasing consumer expectations and demand for prescription medicines in the context of substantive cost constraints. Even though the PBS has an uncapped budget, overall government resources allocated to health care are limited. Spending in one area may mean less resources are allocated to other health areas.(210) Controlling government expenditure on the PBS while maintaining social equity and access to 'essential medicines' is at the centre of an ongoing public debate.

2.4.1 High cost, highly targeted medicines

The definition of "high-cost medicines" is pivotal to the present work. However, the concept of "high-cost medicines" has not yet been clearly defined internationally. 'Expensive' or 'high cost' medicines (HCMs) can be generally described as: (i) those with modest acquisition cost but used in high volume; or (ii) very high cost medicines for which even limited usage might create budgetary pressure.(211) The definitions of HCMs may vary depending on the setting and the perspective of the person or group making the decisions. Cyclosporin and erythropoietin, (US$4,000 to US$6,000 per patient per year, 1994) have been referred to as HCMs.(166, 180) Foscarnet (a monoclonal antibody) and granulocyte colony-stimulating factors were also viewed as HCMs.(212) "Expensive treatments" have been defined as those costing more than £2,000 per patient per year, such as growth hormone and cyclosporin, in the context of primary care in the United Kingdom.(213) More recently, drugs such as imatinib (Glivec®), drotrecogin alfa (Xigris®), and enfuvirtide (Fuseon®) were described by Kleinke as "supremely expensive".(214) Biopharmaceuticals, generally ranging in cost from US$6,000 to US$10,000 (or

greater than US$5,000) per patient per year, have been described as "high-cost", or "high-dollar" therapies by Willcuts.(174, 215)

In Australia, high cost pharmaceuticals have been defined by Victorian public hospitals as those with an acquisition cost of greater than A$1,000 per treatment episode.(216) This definition of HCMs includes drugs provided by the Highly Specialised Drug Program (described in Section 2.3.1.1), and those with an acquisition cost greater than A$10,000 per patient per treatment course.(217) Under the PBS, the general concept of a costly pharmaceutical is a medicine for which its total use is expected to cost more than A$5 million a year. Once such a drug has received a positive recommendation from the PBAC, its subsidy needs approval by the Commonwealth Department of Finance and Administration, or by the Cabinet if its total use is expected to cost more than A$10 million a year.(218)

The Australian government has subsidised a number of 'high cost' drugs under its Highly Specialised Drug Program since the 1990s. However, in recent years, there has been an increasing number of highly effective but 'expensive' medicines, developed as a result of the biotechnology revolution, that could benefit *community based* patients (i.e. drugs that can be administered without the use of specialist facilities). A key feature of these new medicines, in comparison to traditional small molecules medicines, is that they are more likely to be "targeted" to particular sub-sets of patients. These patients might be identified by specific biological markers, disease activity characteristics, genotyping, or insensitivity or adverse reactions to more conventional alternatives.(94) Many of the new therapies are so expensive that, without financial support, access to them is a practical impossibility for the very greater majority of people. A well-known example of such drugs subsidised by the

Australian government was trastuzumab (Herceptin®) in 2001. The PBAC had advised against listing Herceptin®. However, extensive media interest and patient lobbying led the government to subsidise trastuzumab outside the 'normal' PBS mechanisms by creating a special program that was implemented on 1 December 2001. It has been argued that alternative models of access are needed given the high unit costs of these new biological agents, because they may only be cost-effective in a subgroup of patients with a disease, that is, those most likely to respond and benefit from the therapy and in whom, therefore, cost-effectiveness has been shown.(94)

As a result of the competing pressures and interests, novel changes to the process of gaining PBS subsidy as well as arrangements for access were introduced for those specialised, "high unit cost" medicines considered to be used optimally and cost-effectively when targeted to subgroups of patients ("target patient population"). These changes are set to have far reaching consequences for publicly funded formularies such as the PBS that aim to provide citizens with universal access to important, cost-effective, but at times very expensive medicines. The controlled access scheme established and evolving for HCMs in Australia, described in the following section, is an attempt to find a balance between the often competing health, economic, societal and ethical demands while maintaining the sustainability of the PBS.

2.5 Access to high-cost, specialised medicines: Biological anti-rheumatic medicines

A summary of this section has been published as an editorial ("*Access to high cost drugs in Australia – Risk sharing scheme may set a new paradigm*". BMJ 2004; 329:415-416)

Healthcare payers cannot afford to provide every medicine for all citizens without limitation, particularly for a national health system such as in Australia, where health services are heavily subsidised by tax revenues. In recent years, the PBS has established complex controls to target more precisely subsets of individuals for subsidised access to particular HCMs. The approach depends critically on the identification of a sub-group of patients in whom the drug is cost-effective compared with the main available treatment (i.e. "target patient population", as noted). As described in Section 2.3, PBS criteria for access are based on evidence of clinical and cost effectiveness of the drug as evaluated by the PBAC. In addition, an innovative, collaborative model is increasingly used by the PBAC to enable the subsidy of expensive medicines.(85, 219) The complex arrangements for access to HCMs and the stakeholder collaborative model are described below.

2.5.1 Arrangements for access to high cost medicines under the PBS

HCMs are 'authority required' pharmaceutical benefits under the PBS, i.e. prior approval is required before prescribing by physicians. A set of comprehensive arrangements established by the PBAC to control and closely monitor the subsidised access to HCMs is, in general, similar to the arrangements for access to medicines under the Highly Specialised Drugs Program, and involves:

1. Prescribing by medical specialists who must provide documentation to support the patient's eligibility;

2. Satisfying eligibility criteria that codify the detailed clinical features that qualify the patient for access (e.g. severity of the disease);

3. Providing evidence of prior exposure to effective, less expensive alternative medicines but with inadequate response or lack of tolerability;

4. Providing evidence that the patient has a specific molecular disease target or marker that predicts a good treatment outcome if such a marker has been identified;

5. A written application for an 'authority required' prescription for the medicine;

6. An assessment of the patient's response to the treatment prior to approving continuation of therapy;

7. A requirement that patients sign an agreement ('Patient Acknowledgement Form') prior to starting treatment to acknowledge that the PBS-subsidised treatment will cease if sufficient improvement is not achieved; and

8. Risk sharing arrangements between the government and the pharmaceutical company sponsor such as price-volume agreements or tiered pricing arrangements. Risk-sharing arrangements have been increasingly used by the PBS in recent years. Under these arrangements, the price of a drug is influenced by forecasted usage volume. Drugs used in excess of utilisation estimates might attract a lower price, or sponsoring pharmaceutical companies may agree to fund drug usage when expenditure exceeds a certain level.(85, 134)

The eligibility of individual patients for initiation or continuation of treatment is assessed by Medicare Australia, a government statutory authority which administers the PBS, as noted. This restricted access scheme exerts unprecedented control over clinical practice by third parties, namely, the PBS and Medicare Australia. Examples of specialised drugs that are controlled by such access schemes under the PBS include the anticholinesterase drugs in the treatment of Alzheimer's disease (around A$2,000 per patient per year); iloprost trometamol for the treatment of pulmonary hypertension (around A$13,000 per patient per year); interferon beta-1a and glatiramer acetate for the treatment of multiple sclerosis (each at around A$14,000 per patient per year); interferon alfa-2b, imatinib (Glivec®) for the treatment of chronic myeloid leukaemia (around A$45,000 per patient per year; subsidised by the PBS since December 2001); gefitinib (Iressa®) for the treatment of non-small cell lung cancer in patients with evidence of an activating mutation in the epidermal growth factor receptor gene (more than A$50,000 per patient per year; subsidised by the PBS since December 2004); etanercept for the treatment of juvenile chronic arthritis (around A$20,000 per patient per year, subsidised by the PBS since July 2003); etanercept, infliximab, adalimumab, and anakinra for the treatment of rheumatoid arthritis (each at around A$20,000 per patient per year; first subsidised by the PBS in August 2003); and infliximab and etanercept for the treatment of ankylosing spondylitis (subsidised by the PBS since 2004).

2.5.2 Collaborative Decision-making Model

The PBAC developed and used a collaborative model to assist in achieving subsidy of the biological agents for the treatment of rheumatoid arthritis (RA).(85, 219) This innovative approach involved the key stakeholders in the relevant medical specialty (namely, rheumatologists as represented by the Therapeutics Committee of the

Australian Rheumatology Association), and representatives from the pharmaceutical companies. These key stakeholders were consulted by the PBAC to help establish reasonable restriction rules that would govern access to subsidised treatment in a manner consistent with cost-effective use of these drugs. Together this group addressed issues of medical need, cost, safety, effectiveness, cost-effectiveness, and the arrangements by which these drugs might be accessed under the national drug subsidy system. The relevant consumer organisation (the Arthritis Foundation of Australia) supported the concept of 'restricting access to medicines of high cost' and was involved extensively in lobbying activities. The unique consultation process that achieved subsidy of biological agents in Australia has set a new paradigm for subsequent decisions on pharmaceutical benefits.

The outcomes of purported innovations to the PBS subsidy processes and targeting access to sub-sets of patients for particular HCMs need careful evaluation. Such policy-oriented and outcomes research is critical for driving improvements in access schemes, such as those being introduced under the PBS. However, systematic, in-depth evaluation has been limited to date, which is surprising given the societal significance of the PBS and its cost to government and the taxpayer.

2.5.3 Access to medicines for rheumatoid arthritis

The issue of subsidised access to medicines for the rheumatic diseases came into focus with the introduction of a biological group of drugs ('biologicals') for the treatment of RA: etanercept, infliximab, adalimumab and anakinra. Cost is now one of the factors physicians have to consider more carefully when selecting treatments for patients with RA. This section describes the arrangements for access to

biologicals for RA, a representative example of the evolving approach for access to HCMs under the PBS.

RA is a chronic inflammatory disease that is characterised by joint inflammation and destruction, progressive disability, and increased mortality.(220) Joint damage occurs early in the disease process; 75% of joint erosions occur within the first two years.(221, 222) Approximately 50% of patients with RA are expected to experience enough loss of function to cause work disability within 10 years after disease onset,(223) and the disease may be associated with depression and other psychological effects.(224, 225) Some patients may require surgery to correct structural joint damage.(226) Therefore, RA presents a profound health and socio-economic burden.(227) There is no cure for RA. The goal of current treatments is to control disease activity, alleviate symptoms, maintain physical function, optimise quality of life, slow the rate of joint damage and, ideally, induce a remission.(228) RA has been treated with medicines of relatively low cost, such as methotrexate (~A$50-$100 per year) – the first-line treatment for RA and the current standard of care against which new drugs for RA are evaluated and compared; and leflunomide (~A$1200-$1900 per year) – introduced as an 'authority required' drug for the treatment of RA in 2000, the first new drug that had been approved in over a decade.

Biologicals subsidised by the PBS include three tumour necrosis factor-alpha (TNF) inhibitors, etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®), and an interleukin-1 receptor antagonist, anakinra (Kineret®). Etanercept was the first agent subsidised by the PBS since August 2003. Biologicals are indicated for the treatment of established, active RA in adult patients unresponsive to treatment with traditional disease-modifying anti-rheumatic drugs

(DMARDs). Biologicals have been shown to improve functional status, reduce radiographic progression, and improve measures of outcome including a marked reduction in the concentrations of inflammatory markers. These therapies also improve the quality of life of patients.(229-232) However, these agents are substantially more expensive (approximately A$20,000 per patient per year) than conventional anti-rheumatic drugs, and there remain some uncertainties regarding long-term safety, including a possible risk of lymphoma and rare, but serious infections.(233)

In Australia, there were well-founded concerns about the potential cumulative expenditure on these medicines as they are indicated for a prevalent chronic condition. This likely long-term use contrasts with shorter term, expensive therapies for serious 'end-of-life' conditions such as cancer where similarly expensive medicines are available. The cumulative cost of these biologicals over the longer term adversely affects their cost-effectiveness. Similar to other HCMs, prescribing of the biologicals is 'authority required' under the PBS in an attempt to balance the benefits, risks, and costs (particularly when used in chronic conditions of relatively high prevalence). Prescribing rights are restricted to specialist physicians, and a risk-sharing arrangement is in place between the government and the sponsors. Subsidised access to biologicals is restricted to a small proportion of patients who have not been adequately controlled using conventional DMARDs and who meet specific criteria for starting and continuing these medicines (Table 2.3). The PBS restrictions define an eligible patient for commencing subsidised biologicals as one having a total of at least 20 'active' (swollen and/or tender) joints or a total of 4 active major joints e.g. knees, together with an elevated blood concentration of inflammatory markers (erythrocyte sedimentation rate of > 25 mm/hour or C-reactive protein of > 15 mg/L). Patients are required to have had an adequate trial of

DMARDs via a step-up sequence that includes methotrexate (specified minimum dosage of 20 mg/week), a combination of three DMARDs (including methotrexate of at least 7.5 mg/week) for at least three months, and leflunomide (with or without methotrexate) or cyclosporin for a further three months (Table 2.3, Figure 2.4). Regulating access to biologicals is more complex than for other HCMs because of the availability of several effective, biological agents. An 'interchangeability' rule was introduced in December 2004 (Table 2.3) that allows eligible patients to trial an alternate biologic without the need to re-qualify against the initial criteria as there is encouraging evidence that failure to respond to one agent does not predict failure with another.(234)

Table 2.3 Access arrangements for biological agents for the treatment of RA under the PBS

	Authority requirements

Criteria for initiating treatment	• Severe active disease:
	  ▫ elevated concentrations of inflammatory markers (ESR > 25mm/hour or CRP > 15mg/L)
	  ▫ swollen and tender joints – a total of > 20 joints, or > 4 major joints (elbow, wrist, knee, ankle, shoulder, hip)
	• A record of rheumatoid factor positive status (this requirement was removed as of June 2005)
	• Failure to achieve adequate response to a step-up sequence of treatment with conventional DMARDs:
	  ▫ monotherapy with methotrexate (20 mg per week)
	  ▫ a combination of methotrexate (> 7.5 mg per week) and 2 other DMARDs for at least 3 months
	  ▫ leflunomide, leflunomide with methotrexate, or cyclosporin for at least 3 months
	• Evidence of intolerance or contraindication to DMARDs
	• Patients required to sign a 'Patient Acknowledgement Form'
	• Treatment is approved for 16 weeks only (treatment of 22 weeks is approved for infliximab)

A patient agreement process	• A Patient Acknowledgement Form to be signed by patients to acknowledge that PBS-subsidised treatment will only continue if the predetermined response criteria are achieved at 12 weeks

Criteria for continuing treatment	• Clinical outcomes are evaluated according to predetermined quantifiable criteria at 12 weeks:
	  ▫ Reduction in concentrations of inflammatory markers, ESR < 25 mm/hour, or CRP < 15 mg/L, or 20% from baseline levels
	  ▫ Reduction in the total number of joint count by 50%

'Interchangeability' (introduced December 2004)	• Patients approved to commence PBS-subsidised biological treatment are allowed to switch to an alternate biological agent at any time
Restricted prescribing rights	• Prescription only by specialist rheumatologists initially. Prescribing rights were extended to clinical immunologists with expertise in the management of RA as of February 2004
'Risk-mitigation' arrangement	• Annual PBS expenditure for the tumour necrosis factor inhibitors group was predicted to be up to A\$140 million • Expenditure above this figure to be covered by the sponsoring pharmaceutical companies (details not clear from public documents)

CRP = C-reactive protein; DMARDs = Disease-modifying anti-rheumatic drugs; ESR = erythrocyte sedimentation rate; PBS= Pharmaceutical Benefits Scheme; RA= Rheumatoid arthritis
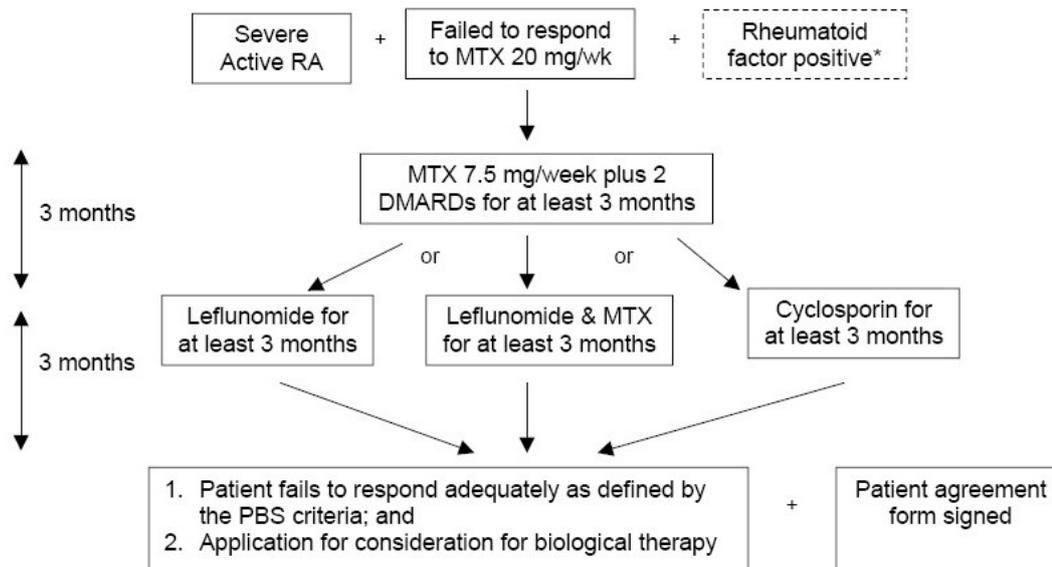
RA = rheumatoid arthritis
MTX = methotrexate
DMARDs = disease-modifying anti-rheumatic drugs
*The requirement for 'rheumatoid-factor-positive-status' was applied from Aug 2003 to May 2005

Figure 2.4 Eligibility criteria for initiating biological treatment via the PBS for rheumatoid arthritis

Etanercept, adalimumab, and anakinra, given subcutaneously as self-injections, are supplied by community pharmacies as PBS benefits under Section 85, while infliximab, administered by intravenous infusion, is supplied through public and private hospitals under the Highly Specialised Program (Section 100).

The Australian community waited more than two years from the time the first biological agent, etanercept, was approved for marketing (2000) until it became available as a subsidised medicine through the PBS in August 2003. The delay in approving subsidy of these drugs is illustrative of the difficult decisions government bodies, industry, clinicians, patients and the public as stakeholders increasingly will

have to make about new targeted therapies that, while not life-saving, have the potential to improve a patient's qualify of life.

The access scheme for biological anti-rheumatic drugs for the treatment of RA has been chosen for the present research program for several reasons: their recent subsidisation by the PBS, the innovative features of the subsidy arrangements, the evolution of the arrangements, the controversy surrounding this subsidy, the unique stakeholder collaboration to enable this subsidy, and the complexity of this access scheme relative to those for other medicines (including other HCMs). Evaluation of programs and policies is a critical part of a continuous quality improvement philosophy,(235, 236) as discussed in Chapter 1. Interventions that regulate access to, and utilisation of, pharmaceuticals may have unintended negative outcomes,(162) thus consideration and evaluation of their effects on clinical and economic outcomes are especially important.

2.6   Australia's National Medicines Policy

As described in Chapter 1, efforts by the World Health Organisation (WHO) provided the impetus for governments to implement national policies to ensure rational drug use in their countries.(16) The WHO recommends that all countries formulate and implement a national medicines policy to guide the access to, the quality and rational use of medicines.(237) National medicines policies should define national goals and objectives for the pharmaceutical sector, set priorities between competing objectives, and identify possible strategies to meet those objectives (Section 1.2). Australia was the first developed country with an official, comprehensive national medicines policy, *Australia's National Medicines Policy*, which was formally launched in 1999. The National Medicines Policy was developed collaboratively with

all interested parties and included consumers, health professionals, the pharmaceutical industry, and government.(114) The national goal and the overall aim of the National Medicines Policy is to "*meet medication and related service needs, so that both optimal health outcomes and economic objectives are achieved*".(238) The policy provides an integrated framework for considering pharmaceutical issues. The four pillars of the policy (http://www.nmp.health.gov.au) are interdependent (Figure 2.5),(116) consisting of:

- "Medicines meeting appropriate standards of quality, safety and efficacy". The quality, safety, and efficacy of medicines are regulated by the TGA. Medicines are evaluated by the ADEC (Section 2.2). Post-marketing surveillance is conducted by the Adverse Drug Reactions Advisory Committee.

- "Timely access to the medicines that Australians need, at a cost individuals and the community can afford". This pillar aims to ensure that cost is not a major barrier to patients' access to medicines. Timely, affordable access to necessary medicines is deemed necessary to support the wise use of medicines, and thereby improve the health of Australians. The PBS is the major means of providing subsidised access to medicines (Section 2.3).

- "Maintaining a responsible and viable medicines industry". Since 1987, Australia has established the Pharmaceutical Industry Development Program, which is known as the Pharmaceuticals Partnership Program from 2004.(239) The viability of the industry is assured by providing remuneration for subsidised products and giving incentives by the Commonwealth Department of Industry, Tourism and Resources. The pharmaceutical industry has an important responsibility to develop Consumer Medicines Information.

- "The quality use of medicines" (QUM) is the central pillar of the policy, enabled and supported by the other three components – advised by the Pharmaceutical

Health and Rational Use of Medicines Committee. The concept of QUM means, for both the *society as a whole* and *individual patients*,

- selecting management options wisely

- choosing suitable medicines if a medicine is considered necessary

- using medicines safety and effectively

The significance of Australia's National Medicines Policy is that it recognises the interdependence and tensions inherent within the objectives of the policy. Examples of the tensions inherent within the framework include the balance of maintaining medicines at affordable costs and a viable pharmaceutical industry, and the balance between meeting the individual's and the community's needs.

Figure 2.5 Australia's National Medicines Policy illustrating the interdependence of the four pillars

The concept of QUM promotes optimal use of medicines one step further than that provided by the WHO definition of 'rational use of medicines', which recommends that "*patients are to receive medicines appropriate for their clinical needs, at appropriate doses, for an adequate duration, and at the lowest cost to the individual, the health system, and the community*".(240) The QUM concept includes monitoring of outcomes and solving medication related problems. In addition to 'rational use of medicines', QUM also recommends that non-pharmacotherapies should be considered as management options thus, in effect, maximising the health outcomes by selecting from all the evidence-based options and, as a by-product, enhancing the likelihood of achieving 'value for money' of medicines. QUM also recognises the fundamental role of consumers and emphasises the importance of 'partnership' between healthcare providers, medical practitioners, allied health professionals, patients, and the pharmaceutical industries to achieving 'quality use of medicines'. There are six building blocks that are considered to be the essential requirements of any policy or program that enables the 'quality use of medicines' in practice (116):

- Policy development and implementation

- Facilitation and coordination

- Provision of objective information and assurance of ethical promotion of medicines

- Education and training

- Provision of services and appropriate intervention

- Strategic research, evaluation and routine data collection

2.7 Hypothesis, Research Objectives, Study Design

Restrictions on access to, and use of, medicines have clinical, economic, and ethical effects, both intended and unintended,(121) as noted. The scarcity of quality evaluations of the outcomes of authority-required prescribing in Australia should be of concern to patients, healthcare professionals, administrators, and others since this policy is commonly used. To date, there has been limited examination of arrangements for access to HCMs through national drug subsidy systems. *There are no published data on perceptions of the various parties with respect to arrangements for PBS-subsidised access to HCMs, or studies examining stakeholder consultation processes to achieve PBS-subsidy of HCMs.* Consideration of the ethical dimensions of such schemes has also been minimal. Further, no Australian studies have examined the controlled access to medicines in light of the National Medicines Policy. The present research aimed to redress these gaps by examining in detail the access to HCMs via a public drug subsidy system, using access to biological anti-rheumatic drugs via the PBS as an example. Findings of this work are instructive in informing the debate concerning the principles and processes that might underpin equitable, efficient, and effective access to expensive pharmaceuticals under the PBS or similar access systems and ultimately, optimal health and economic outcomes.

The overarching hypothesis for this research is:

"*The arrangements for access to biological anti-rheumatic drugs via the Pharmaceutical Benefits Scheme are consistent with Australia's National Medicines Policy*".

The National Medicines Policy was selected as the framework for this evaluative research because it is the national framework that clearly defines the overriding goal of medical care as well as the specific goals and roles of the different players in the Australian health system, with respect to medicines.

The principal goal of this research was to carefully examine the arrangements for access to biological anti-rheumatic drugs so as to understand the strengths and weaknesses of these arrangements and ways in which systems of access could be improved.

The specific aims of this research were to:

1. Explore perceptions and experiences across a range of stakeholders with respect to:
   - the controlled access to biological anti-rheumatic drugs
   - collaboration between the relevant stakeholders

2. Examine the implementation of PBS criteria (namely by Medicare Australia), including the issues that emerged during the application process,

3. Examine the effects of the controlled access to anti-rheumatic biologicals on resultant health outcomes,

4. Analyse the utilisation of anti-rheumatic biologicals and compare these data to the forecasts on usage,

5. Examine the effects of the controlled access to anti-rheumatic biologicals on patterns of use of conventional disease-modifying anti-rheumatic drugs, and

6. Critically evaluate the access to anti-rheumatic biologicals from an ethical perspective

This work used a combination of qualitative and quantitative research methods to examine the PBS access scheme for biological anti-rheumatic medicines. Quantitative and qualitative research methods are often used in a complementary fashion.(241, 242) Quantitative research methods are used to collect structured data or numerical measurements from a large number of respondents based on a prior understanding of the nature of the issue being investigated. This approach provides the incidence of various events, the relationship between variables, and comparison and measurement of outcomes. Qualitative research is particularly useful to examine and probe into issues that are complex, contextual and influenced by the interaction of social factors. Understanding of the views and experiences of stakeholders on an innovative approach to managing access to HCMs is crucial, and complements quantitative data to provide a more complete picture of the access scheme. Such a broad assessment is important when examining possible or actual interventions designed to improve the scheme. Details on the methods used for data collection and analysis are included in each chapter.

The findings of qualitative and quantitative studies are examined from the perspective of the National Medicines Policy in order to identify novel and more relevant methods to improve the access scheme and its implementation. This research has wider relevance, as access to HCMs is increasingly challenging internationally. It is hoped that the findings from this work will provide a foundation and guide to suggesting, evaluating and implementing changes in the systems of subsidised access to expensive but important medicines in Australia and elsewhere and also provide directions for further research.

3. STAKEHOLDER PERSPECTIVES ON ACCESS TO ANTI-RHEUMATIC BIOLOGICAL MEDICINES IN AUSTRALIA: A QUALITATIVE STUDY

This chapter reports an investigation into perceptions of the access to anti-rheumatic biological medicines in Australia using qualitative research methods. Views and experiences across a range of relevant stakeholders associated with the controlled access to anti-rheumatic biologicals under the Pharmaceutical Benefits Scheme, and their opinion on the collaboration between stakeholders were explored.

3.1 Introduction

There is limited research exploring the perspectives of decision makers and stakeholders on how to prioritise decisions about drug reimbursement in Australia at a national level. It is important to understand the views of stakeholders about existing arrangements for access to high-cost medicines (HCMs) operated through the Pharmaceutical Benefits Scheme (PBS), and on the stakeholder consultation processes used to develop arrangements for subsidised access to HCMs. A representative example is the tumour necrosis factor (TNF) inhibitors (the "biologicals") for the treatment of rheumatoid arthritis (RA) as described in the previous chapter. Valuable insights into the recent developments in targeting access to TNF inhibitors can be gained by exploring the perceptions and experiences across a range of relevant stakeholders. The views, attitudes, concerns, and level of support for these arrangements by the stakeholders are critical determinants for a successful implementation of any interventions. Understanding such issues and concerns is likely

to lead to better management of access to, and use of, important but expensive medicines under the PBS or similar subsidy systems.

3.2   Stakeholders associated with access to anti-rheumatic biologicals under the PBS

Stakeholders are individuals, groups and organisations who have interests in a decision and the potential to influence related decisions.(243) Stakeholders in the pharmaceutical market have been identified,(238, 244) and include:

- Governments and their agencies (e.g. Department of Health and Ageing, Medicare Australia, Department of Industry, Tourism and Resources)
- Citizens – who have a double role as patients and taxpayers
- Healthcare professionals
- Pharmaceutical industry

Stakeholders of the pharmaceutical sector are focused on the common objective of equity and ease of access to safe, effective and high-quality pharmaceutical products, ultimately improving health outcomes.(244) There are, however, some competing objectives. As taxpayers, citizens wish to control public expenditure for healthcare, but as patients, they may demand access to new and more expensive drugs, which may not be the most efficient or equitable use of resources from a societal perspective. Healthcare professionals, particularly prescribers, want to use safe and effective drugs but may also want to preserve professional privileges and may resent constraints on their prescribing. The pharmaceutical industry aims to provide high-quality drugs but also needs to do so in a manner that meets its primary aim of profitability in a competitive market. Additionally, it is in the interests of pharmaceutical companies to have their products used successfully and safely.

Governments which represent both the citizens and industry want a balance between the costs, optimal healthcare, and at the same time economic growth.(244)

In order to collect the views of stakeholders, the parties which were involved and their roles in the decision to subsidise etanercept (the first anti-rheumatic biological via the PBS) needed to be identified. From these parties, 'key informants' provided information for the investigators regarding their participation and contribution to the process leading to the listing of etanercept, and identified other important players engaged in the process. This process enabled identification of relevant stakeholders (Table 3.1) who were then invited to participate in the present study. In the period between the marketing approval of etanercept in 2000 and the recommendation for subsidisation at the end of 2002, protracted discussions took place between three major stakeholder groups: the Pharmaceutical Benefits Advisory Committee (PBAC), the Australian Rheumatology Association Therapeutics Committee, and the sponsor of etanercept. A brief description of roles and activities of each stakeholder group by these 'key informants' is summarised in Table 3.1. Although not directly involved in the stakeholder consultation process, there was considerable support and lobbying activities by consumer representatives (namely the Arthritis Foundation of Australia) for 'targeted' access to high-cost biologicals. Activities undertaken by the consumer organisation, as described by 'key informants', are summarised in Table 3.2. It is known that the sponsoring pharmaceutical company had been supportive of these activities and employed public relation companies to assist with awareness raising campaigns. Clearly, such publicity is likely to increase patient demand and influence prescribing practices. However, it was not clear from public documents whether this consumer organisation received any funding from the company for these activities.

Table 3.1 Key stakeholders involved in the PBS decision to subsidise anti-rheumatic biologicals

Stakeholders	Roles and activities identified
Pharmaceutical Benefits Advisory Committee (PBAC)	• Assess the evidence for the medicine's cost-effectiveness compared to other existing therapies (including both pharmaceutical & non-pharmaceutical interventions) • Give advice to the Health Minister about which medicines should be made available as pharmaceutical benefits
Australian Rheumatology Association Therapeutics Committee	• Represent the rheumatologists and their patients • Provide expert advice to the PBAC regarding proposed eligibility criteria for access • Prepare a list of toxicities and contraindications of disease modifying anti-rheumatic drugs
Pharmaceutical industry for etanercept	• Involved in discussions with the PBAC and the rheumatologists • Provide data on the efficacy, safety and cost of etanercept to the PBAC • Involved in discussions with the consumer organisation (the Arthritis Foundation of Australia)

Table 3.2 Activities by the Arthritis Foundation of Australia during the PBS decision-making process for subsidising anti-rheumatic biologicals

Activities	Details
Interactive web-cast (2001)	• Discussion about 'targeting' access for patients with severe rheumatoid arthritis who need to meet certain criteria • Made available on its website
Hand-written letter writing campaign	• Letters were sent to key bureaucrats, and to a radio station hosted by a well-known radio announcer
Liaison between patients and the bureaucrats	• A number of patients acted as advocates to speak to politicians and bureaucrats about inadequacies in the management of their disease
Access Economics report (2001)	• Prepared a report entitled: "The Prevalence, Cost and Disease Burden of Arthritis in Australia"

Stakeholders, for the purpose of this study, were defined as individuals or groups of people having the potential to influence the decisions on the access arrangements, and those affected by the PBS-restrictions or engaged in the implementation of PBS-restrictions. This definition thus includes the following parties in the case of anti-rheumatic biologicals:

- Rheumatologists

- Government advisors: e.g. members from the PBAC, the Pharmaceutical Benefits Pricing Authority (PBPA), the Economic Sub-Committee (ESC), and the Drug Utilisation Sub-Committee (DUSC)

- Respective pharmaceutical companies sponsoring etanercept, infliximab, and adalimumab

- Patients with RA

- Consumer representatives

- Public servants (administrators and staff of Medicare Australia and Pharmaceutical Benefits Branch of the Commonwealth Department of Health and Ageing)

3.3   Aims and objectives

The aims of this study were to explore the perceptions and experiences of stakeholders (including both stakeholders engaged in the stakeholder consultation process, and those who were not) with respect to the access to HCMs in Australia, and their views on the collaboration between stakeholders, focusing on access to the anti-rheumatic biologicals as an example.

The specific objectives were to explore stakeholder opinions with respect to the:

- PBS access arrangements for TNF inhibitors

- application process to gain PBS-funded access

- collaboration between stakeholders: before and after PBS-subsidy

- educational materials, activities, and services that were provided, and suggestions about what would have been beneficial in the view of the participants

The purpose of the study was to use the identified concerns as a basis from which to recommend future processes and approaches of access to HCMs with a view of system improvement.

3.4 Selection of methods

The objectives of the study were such that they could best be addressed through the use of qualitative research methods, since we were searching for meaning and seeking to enhance our understanding of the different stakeholder views.

3.4.1 Qualitative research methods

Qualitative research methods have been used in the social sciences, and more recently have had an increasing role in the area of health services and policy research.(245-247) Qualitative methods offer the most appropriate approach to explore complex attitudes and behaviour, and to search for understanding and meanings from a broad social context rather than by measurement or generalisation from the traditional quantitative methods.(247, 248) These methods can offer descriptions that are usually rich in detail and provide much deeper insights into 'why' and 'how' phenomena occur. Findings can yield detailed and holistic views that add to knowledge or increase the confidence in existing knowledge. Thus they can be used to enhance the development and improvement of quality measures.(246) Using qualitative techniques, researchers are able to gain an in-depth understanding,

explain, discover, explore, describe, and learn from participants about their experiences, perceptions and concerns with respect to a certain event, an issue, or a process.(248-250) Qualitative research allows "*people to speak in their own voice*".(251) The usefulness of qualitative research is not determined as much by the number of participants who have a particular opinion, as by the meanings behind the words used, often reflecting a rich range of opinions and ideas.(246, 252)

In comparison with quantitative methods, in general relatively small sample sizes are used in qualitative research. The aim of sample selection in qualitative methods is to reflect the population of interest, not to identify a statistically representative set of participants that is generalisable to the whole population, or probability based.(246, 252) Thus, the sampling strategy is often purposive or theoretical rather than statistically representative. Including individuals from the different stakeholder groups is also a method of triangulation (namely, triangulation of data sources).(253) Triangulation is an important research method that ensures comprehensiveness of data analysis rather than being a test of validity (further discussed in Section 3.5.6).(246, 253) Some of the main qualitative research methods currently used in health services and policy research include interviews, focus groups, observation, and participatory action research.

3.4.2 Semi-structured interviews

Semi-structured interviews were selected to collect the perceptions of participants in this study. Semi-structured interviews in general involve the use of a flexible topic guide with open-ended questions to explore experiences and attitudes, and allowing the interviewer or interviewee to pursue an issue in more detail. Other styles of individual face-to-face interviews are: (i) structured interviews – interviewers ask

structured questions in a standardized manner, and (ii) unstructured – one or two issues explored in much greater detail.(254) Semi-structured interviews have been extensively used to explore the views of patients and health managers about priority setting in healthcare.(255-257) The semi-structured interview approach has the following advantages: ideas and discussion are allowed to develop, the participants are given the opportunity to focus on topics important to them within the framework of the research question, and the investigator has the opportunity to pursue emerging themes and seek clarification.(246) Furthermore, this form of enquiry was chosen so as to ensure that all stakeholder groups had an opportunity to share their individual experience in a confidential exchange at a time that best accommodated their busy schedules.(248)

In a qualitative research interview the aim is to elicit the interviewee's own framework of meanings and views, and avoid imposing the researcher's assumptions. Interview methods require researchers to be flexible and open to concepts and variables that emerge which may be different from those anticipated. Further, the interviewer must have sufficient training and experience to know when a response deserves probing while also being able to focus the interviewees to discuss their knowledge and attitudes relevant to the question in the amount of detail required.(248, 254)

3.5 Methods

3.5.1 Setting

Anti-rheumatic biologicals were listed by the PBS in August 2003. The interviews were conducted in Australia between September 2004 and June 2005. The views of participants relating to issues around the access to HCMs were explored, focusing on the recently established access to TNF inhibitors via the PBS – a national community-based scheme, rather than the access to HCMs in hospital settings. The author (CL) conducted all the interviews.

3.5.2 Piloting & instrument development

Qualitative research is often undertaken through an iterative approach, in particular where the impact of implementing new access criteria on practice is unknown. The scope of such a study is not specified in advance but is developed iteratively as is the content of the study. The purposes of this first phase were three-fold: (1) to elicit a basic viewpoint from one member of each of the four major stakeholder groups with a vested interest in any new policy about provision of medicines, in order to confirm where further exploration should take place in the subsequent interviews; (2) to provide an opportunity for the author to initiate steps in understanding the issues to be further researched; and (3) to confirm items to be included in an interview guide for use in the subsequent interviews.

Participants for the pilot phase were selected on the basis of their primary membership of different stakeholder groups with respect to the controlled access to TNF inhibitors. These included:

- A medical practitioner (rheumatologist)

- A health advisor to the government

- An employee of a pharmaceutical company

- A patient (who had used a TNF inhibitor)

A finite number of key stakeholder representatives were involved in the PBAC decision-making process that formulated the arrangements for access to TNF inhibitors. Due to being a limited number, they were purposively *not* invited in this pilot phase of the study. This was done in order to preserve the exploration of their perceptions until the subsequent, main study. For example, an employee of a pharmaceutical company was included in the pilot phase to give views of the industry but was not from a company that marketed TNF inhibitors. All interviews were recorded with a digital voice recorder. Notes were taken during and after the interview. Interviews were transcribed verbatim and proof-read for accuracy against audio recordings. Comments by participants about the clarity and relevance of the questions put to them were made and interview questions were refined based on this feedback. The interview transcripts were reviewed carefully in order to enable the next iteration of interviews to focus constructively on where most could be learned. Data analysis (details described subsequently in Section 3.5.6) was conducted and initial results were documented in the form of a publication ("*Recent developments in targeting access to high cost medicines in Australia*". Aus NZ Health Policy 2005; 2:28).

3.5.3 Selection of participants

As previously described, "purposive sampling" is used to identify and include subjects with special characteristics aiming to illuminate the research questions and to maximise gain in knowledge and richness of information.(246) For this study, a theoretical sample of stakeholders was identified as outlined in Section 3.2. All stakeholder groups should be included in order to obtain a well-rounded picture of the access scheme. Individuals from each stakeholder groups were therefore invited to participate in this study.

Purposeful sampling was used to select "information-rich cases" for in-depth study,(246, 249) that is, those individuals involved in formulating the PBS criteria who could shed light on the development and implementation of PBS criteria. Subsequently, a "snowball sampling" technique (246) was used asking these participants to provide leads to further interviewees, thus allowing the objectives to be thoroughly investigated. One nurse participated in the study opportunistically.

3.5.4 Recruitment

The key stakeholders involved in the PBS decision to subsidise anti-rheumatic biologicals as described previously (Section 3.2) were identified as "information-rich cases". Letters of invitation (Appendix 3.1) to participate in the interviews were first distributed to these individuals. Other potential participants (not necessarily engaged in the stakeholder consultation process) were subsequently recommended by these information-rich cases. Patients were invited to participate via their rheumatologists. A separate letter of invitation was prepared for patient participants (Appendix 3.2). The invitation letter outlined the main objectives of the study. Those who responded

positively were contacted, and an interview was arranged to take place in a location and time that suited them. Participant information sheet (Appendix 3.3), consent form (Appendix 3.4) and a demographics questionnaire (Appendix 3.5) were forwarded prior to the scheduled interview. An information sheet containing a brief description of the study, including patient selection criteria (Appendix 3.6) was provided to interested rheumatologists to help recruit patients in this study.

3.5.5 Data collection

3.5.5.1 Interview process

In-depth, face-to-face, semi-structured interviews were used to collect the perceptions of participants. These interviews were conducted between September 2004 and June 2005, in Sydney, New South Wales; Canberra, Australian Capital Territory; and Melbourne, Victoria, Australia. Before the interview, interviewees were given details of how the information was to be used. Due to the confidential nature of the information revealed by the interviewees, emphasis was placed on reassuring each participant that anonymity was guaranteed. All interviewees were asked to declare any potential conflicts of interest, that is, any previous or current advisory role in a pharmaceutical company, or in any other committees or organisations that have a vested interest in the PBS-listings.

Interviews commenced by asking participants to provide a brief description of the participant's role and involvement in the process associated with the access to biologicals via the PBS. This was followed by a discussion of a list of topics contained in an interview guide (Appendix 3.7). The interview guide was used as a prompt sheet to ensure the same topics were covered during the interviews.

Questions were not asked in a standardised manner; this allowed the opportunity and flexibility to not only address the key questions, but also allowed discussion of unanticipated matters. The interview guide was refined and evolved somewhat as the study progressed to allow new concepts that emerged to be included. Interviewees were reminded that it was their thoughts and opinions as stakeholders that were being sought.

Interviews were audio-recorded with the permission of the interviewees. Once the interview was finalised, the dialogue was transcribed. A transcription file included subject identification number, stakeholder group representation, date, other relevant information and special circumstances. Interviewees were asked to review a copy of the transcript. Notes were also recorded by the interviewer during and after each interview. Interviews were conducted with new participants until thematic saturation was achieved (i.e. until no new relevant themes were emerging).(258)

3.5.5.2 Demographic characteristics

The demographics and characteristics of the participants were recorded, including age group, gender, primary stakeholder group represented, and role/position within the organisation.

3.5.6 Data analysis

Interviews were transcribed verbatim by a professional transcriber. Each transcript was verified by the author against the original recording for accuracy. Preliminary data analysis of major concepts arising was conducted after each interview. This allowed identification of issues that required further exploration in the interviews that followed.(259) More interviewees from the different stakeholder groups (a total of six

stakeholder groups forms the 'theoretical sample' of this study as described in Section 3.2) were then recruited using a technique known as 'snowball sampling',(246) thereby leading to theme saturation.

A thematic analysis was carried out using an inductive approach to obtain categories emerging from the data. Comparative analysis was also conducted. This involves comparison of the transcripts with one another to uncover commonalities and linkages that help to identify themes represented in the collective data.(246) De-identified transcripts were imported into QSR NVivo version 2.0 (QSR International, Australia), which was used to manage the qualitative data and assist in the coding of major concepts. NVivo as a data management tool facilitated the inductive process of analysis and comparative analysis. Following repeated and comparative reading of the transcripts,(260) segments (e.g. paragraphs, sentences) were 'highlighted'. The highlighted segments represented concepts and themes arising from the qualitative data. These were then stored under different 'nodes' – the term used in NVivo, as a code, theme, or a label describing the data and to represent the derived meaning – and organised in an hierarchical structure. The emerging themes and coded segments were compared with each other, further redefined, reorganised and a final framework of categories and themes constructed.(259) Identified themes were also explored within and between stakeholder groups. Assimilation and interpretation of these themes formed the basis of the final report.

3.5.6.1 *Validity and reliability*

In qualitative research, validity rests in the extent to which the account accurately represents the phenomena under study. Validity of qualitative research is concerned with both processes of data collection and analysis.(259) Reliability, or "replicability" of the findings,(261) relates to the reliability of the data analysis which can be evaluated by demonstrating that the data analysis process has been systematically performed.(259) The following processes were used to ensure the research was undertaken with methodological rigour:

- Respondent validation – verifying the meaning ascribed to interviewees by offering them the opportunity to review edited transcripts to check that their views had been accurately represented.(262) The results of this study were presented to participants as well as other pertinent stakeholders (e.g. government advisors, public servants, doctors, pharmacists, and consumers) in the context of access to medicines via the PBS for feedback on the validity of the conclusions.

- Negative case testing (deviant case analysis) – the author searched through the data to find cases that ran counter to the findings to enhance our interrogation of the data.(246) This is the conscientious effort to identify data that are inconsistent with the emerging themes. When found, these data were used for refining the emerging conclusion.(253)

- Intra-observer consistency – half of the transcripts were coded on two separate occasions by the author to ensure consistency with the coding.

- Data triangulation – the data obtained from multiple data sources (in the case of this study, interviews with members of different stakeholder and interest groups) were compared.(246, 253) Patterns of convergence to corroborate an overall interpretation of the data were examined. The assumption underlying this approach is that weaknesses of one source will be offset by strengths in

another, and that it is possible to adjudicate between different accounts (e.g. from interviews with government advisors and rheumatologists).(253)

- Researcher triangulation (inter-coder reliability) – multiple researchers shared their interpretations of the data.(262) For this study, half of the transcripts were independently coded by another investigator (RD or KW) according to emerging themes. The researchers then met to examine the analyses in order to reach agreement on categories and identified themes. This process involves cross-checking of coding categories and interpretation of data. Some differences with regard to labelling the themes were found, but agreement was reached on the central meanings. Multiple coding by different researchers also ensured the complete range of ideas existing within the transcripts was fully captured.

- Thematic saturation – continuing to add interviews until no new relevant themes were emerging.(258)

3.5.7 Ethical considerations

Participation in the interviews was voluntary. Participants were provided with a Participant information sheet (Appendix 3.3) which gave a thorough explanation of the purposes of the study, as well as information regarding their rights and confidentiality provisions. The interviewer elaborated on this at the commencement of each interview. All participants signed a consent form (Appendix 3.4) in the presence of a witness (the author). The study was approved by the Human Research Ethics Committees of St Vincent's Hospital Sydney, and the University of New South Wales, Australia.

3.6 Results

3.6.1 Study participants

Forty-three people were invited to participate in the study. Two did not respond, and five declined to participate. Administrators at the Highly Specialised Drug Branch of Medicare Australia who assess patient applications for access to anti-rheumatic biologicals were invited to participate four times over 12 months, but eventually declined the invitation to participate. The main reason given for non-participation was concerns about privacy as these individuals have reviewed individual patient applications for access to the biologicals.

Thirty-six semi-structured interviews were conducted. The demographic characteristics of the participants are shown in Table 3.3. Interviews were of 45 to 80 minutes in duration.

Table 3.3 Characteristics of interview participants (n=36)

		Number of participants
Age group	18-29 years	1
	30-39 years	5
	40-49 years	8
	50-59 years	14
	over 60 years	8
Gender	Male	13
	Female	23
Stakeholder group	Rheumatologist	8
	Patient	6
	Government advisor	5
	Public servant	8
	Consumer representative	5
	Pharmaceutical industry representative	3
	Clinical nurse	1

None of the government advisors, public servants, consumer representatives, or patients had held advisory positions or roles on behalf of a pharmaceutical company. Of the 8 rheumatologists who participated in the study, four had been or were on at least one advisory committee of a pharmaceutical company. Most rheumatologists (7 out of 8) had been in practice for more than 10 years; the number of patients each rheumatologist treated with biologicals under the PBS ranged from 2 to 16. Most patients (5 out of 6) were prescribed etanercept.

3.6.2 Themes

Five major themes emerged, 'resource rationing', 'bureaucracy versus care', 'partnerships and inclusive decision-making', 'education', and 'review of access to HCMs' (Table 3.4). All five themes were related to the perceived fairness of the processes of drug listing and implementation of PBS restrictions, and were essential determinants of support by stakeholders when the access criteria were implemented. Significant variability of responses between different stakeholder groups was not found on most issues. Marked differences were not found in the views of rheumatologists who had held an advisory position with a pharmaceutical company versus those who had not. The major themes that arose emerged from all stakeholder groups. Quotes were used to illustrate the themes presented.

Table 3.4 Summary of themes

Themes	Sub-themes	Key points
Resource rationing	• Definition of target patient population • Individual care versus public good • Timeliness of access to medicines • Patient agreement	• Targeting access supported in general as a necessary form of rationing • Not in agreement on how "target patient population" is defined; some access criteria seen as arbitrary • Tension exists between balancing needs of individual and population
Bureaucracy versus care	• Impact on the use of resources • Impact on rheumatology practice	• Medical care becoming bureaucratic • Increased use of resources by the Department of Health and Ageing, Medicare Australia, at the rheumatologist level • Re-evaluation of previous treatments used by patients; more comprehensive and systematic use of anti-rheumatic drugs
Partnerships and inclusive decision-making	• Collaboration between stakeholders • Stakeholder collaboration – who should be the participants? • Transparency • Communication	• Overall support for stakeholder consultation, seen as a significant step achieved • Communication between stakeholders has increased • Patients/consumers should be directly involved • A need for greater transparency • Wider and more structured consultation is desirable
Education		• More information for patients with respect to controlled access to medicines • Better knowledge of biological medicines and PBS system by health professionals • Medical society has a role in providing clinical information • National Prescribing Service has a role in providing information on the PBS
Review of access to HCMs		Process and outcomes of access schemes should be reviewed, including: • Access criteria • Drug utilisation and health outcomes • Risk-sharing agreement • PBAC process • Administrative expenses

3.6.2.1 Resource rationing

Providing access to expensive medicines through a publicly funded system (the PBS) was seen by all participants as equitable and a feasible approach. HCMs represent a considerable amount of public expenditure and the government is accountable for such spending. Targeting access to HCMs was accepted as a necessary form of "resource rationing". The vast majority of participants acknowledged that there were finite resources available for the possible range of diseases and that the PBS is there to provide access, equitably across all medical areas. Although a view was that in general the government could and should allocate more funds towards health services and medicines. The concept of targeting access to subgroups of patients who most needed treatment and would gain most benefit was in keeping with spending "for value" espoused by multiple interviewees including government advisors, public servants, and pharmaceutical company spokespersons.

> *"The major benefit is that a group of patients with a significant clinical need have been able to get access to a medication that has substantially improved their clinical course and their quality of life and without such an approach they wouldn't have got that in our current system." (government advisor)*

> *"There is a lot of enthusiasm to prescribe drugs [biologicals]. I think the current criteria are limiting the expenditure, which is what they're there for, which I think is a good thing, these drugs should be budgeted. They are very expensive, for the taxpayer. And if they're making a definite improvement in someone's quality of life then we should have it available for people, [but] we don't want to be wasting it." (rheumatologist)*

"I think it [PBS] is a really good system because it means that society is only paying for value. There are so many drugs that you have to pay top dollar for but they're really not having value…" (industry spokesperson)

Consumers, patients, clinicians and industry spokespersons showed appreciation that high-cost biologicals were made available via the PBS. However, most interviewees of these four groups perceived that the primary purpose was to control costs and that strict access criteria reflected PBAC's concern to reduce the risk or likelihood of prescribing outside PBS restrictions ("leakage"). Whilst government advisors and public servants agreed that cost was evidently a consideration that leads to the strategy and practice of rationing, another motive for restricting access in the early stages of PBS access to biologicals was because the long-term safety of biologicals had not been ascertained. Thus, the two major and legitimate goals of limiting access to biologicals, considered by government advisors and public servants, were: (i) making expensive medicines available and affordable to individuals and the community, and (ii) preventing harm by limiting prescribing to those in greatest demonstrable need.

"One [goal] is that they're [government] trying to actually give people access to drugs which otherwise wouldn't be available or couldn't possibly afford as individuals, even though they're doing that in full recognition that it's only a small proportion of the population. By designing these specific restrictions they're just trying to make the drug cost-effective, to allow equitable access of drugs across the whole population. So to give no less or more weight to one disease than another… I think harm minimisation is also part of the component of it by limiting the prescribing habits essentially because access

is somewhat regulated by the group whom they think have the most expertise in that area and are more likely to use the drugs more sensibly." (government advisor)

"…quite specifically the goal is to restrict access … at the very early stage of its life, to restrict [access] in order to protect the public and to make it as close to expansion of clinical trial as possible, and related to real practice… Of course I wouldn't deny for a minute that cost was an important consideration… " (government advisor)

Rheumatologists were also concerned about the long-term safety of biologicals at the time of the study, thus they were in agreement with respect to controlled access in this regard.

"…with the new medication I'm actually cautious about prescribing it, and for that reason I totally support limiting criteria for access to the medication for that reason. And because I think we do need to reserve the medications, expense wise, side effect wise, and experience wise, to a subset of patients with severe disease, who really have no other option." (rheumatologist)

Patients who were treated with biologicals through clinical trials were given special consideration for continued access if they did not meet the eligibility criteria. This was noted as a "strength" of the system and applauded by government advisors and public servants.

Some interviewees proposed that the principles of allocation and access to medicines need to be worked out in greater detail between stakeholders; this needs public discussion, a sub-theme under 'Partnerships and inclusive decision-making' (see Section 3.6.2.3). Further, inequalities of access to HCMs between different hospitals due to capped budgets and decision-making in each individual hospital was identified as an unresolved matter. This was illustrated by the following quotes from government advisors:

"The principle is not set up collaboratively, so I think there is a need to actually be able to get all the stakeholders together and try and come up with other ways of actually allowing access to high-cost drugs and how that could be done."

"I think it's a matter of getting the stakeholders together and looking at other ways of trying to fund these things and that's going to need cooperation between state governments and the Federal Government… there are inequities across the system where the State Government is giving a lot of money to one hospital to give the drug and then the next hospital doesn't get it so it needs to be looked at…"

3.6.2.1.1 Definition of target patient population

All agreed that criteria for access should be based on sound clinical evidence. Participants in general agreed that, in broad terms, criteria such as "clinical need" and the lack of an alternative treatment should govern access to HCMs. However, not surprisingly, interviewees were not in agreement on how an appropriate target patient population should be defined.

Some interviewees suggested broader, initial access. The risk of excessive uptake of biologicals outside the PBS-criteria should be relatively low by using other controls, namely, risk-sharing between sponsors and government via *price-volume agreements*, and the *continuation rule* that limits ongoing access to those who responded to treatment to a clinically meaningful degree; these controls are already in place. On the other hand, some participants proposed the removal of the *continuation rule* as it is ethically challenging to withdraw access to a medicine because it is not effective enough according to an "arbitrary" standard.

> *"I think it causes a lot of grief when you have continuation rules for individual patients. I mean that's the thing that strikes home for me is when you're having a bureaucracy saying you're to stop the drug now. I think that's the cause of much distress for patients and doctors and everyone really, especially if the patient feels that they're well." (government advisor)*

The majority of interviewees, apart from government advisors and public servants, were concerned about the specificity of PBS criteria and how they came about. Some criteria were seen as "arbitrary" and "potentially unfair" because of the lack of published literature supporting the criteria and poor transparency around the rationale of these criteria. A rheumatologist gave his opinion strongly:

> *"I think they [criteria] are really quite restrictive. In particular the restriction to seropositive patients is unfortunate. Secondly, the reliance on laboratory indices is a concern. In some patients their condition is not particularly well reflected in laboratory indices and it puts such an emphasis on reductions, and especially in something like the ESR [erythrocyte sedimentation rate], which is essentially a vague index, is unfortunate … The one which could be*

added to the clinical assessment, in my view, is the patient's own feeling of

wellbeing and change in activity."

There were some "well-deserving" patients who in the view of their physicians met most criteria that warranted access but were denied access (i.e. missing the benchmark). Financial and psychological pressures were often overwhelming for these patients and their families. In some cases, their health deteriorated to the extent that they eventually met defined criteria for severity of their RA and gained access to biologicals.

"…the requirement I think is completely unfair and un-thought through is the

requirement for a positive rheumatoid factor blood test… why would you put

in a faulty clause? So you can end up with people in my situation that

definitely have rheumatoid arthritis, that have tried all the medicines, that

have nearly their whole body affected, and yet they can't access this

medicine that works…so I cannot see why this criteria is in… I mean we're

not just people that have a bit of a sore arm or something. We're people that

can hardly move…that's the other thing that upsets me, that they're getting

people that have suffered so much already who are really, really sick and in

agony, and then they're not helping them. So it seems very heartless to me,

the whole process." (patient)

The requirement to first trial existing, potentially effective but cheaper established therapies was considered to be reasonable by all groups. Limiting prescribing rights to specialist physicians was deemed safe and appropriate given: (i) the expense of the medicines, (ii) the severity of RA in the affected patient population thus the need for specific expertise and experience in RA management, and (iii) in light of

concerns and uncertainty about long-term safety of the biologicals. A patient voiced the predominant view about prescribing effective, cheaper drugs before consideration of biologicals:

> *"I think it's good that people have to have tried all the other cheaper medicines, that's fair enough. Why should the government pay for a really expensive medicine when methotrexate works and also, we don't know yet what the long-term side effects will be. I think that you have to have quite a few joints affected is not unreasonable."*

Not surprisingly, rheumatologists were also in agreement that they are the most appropriate clinicians for treating patients with RA:

> *"I don't think immunologists are the best people to be looking after rheumatoid arthritis. I think sometimes immunologists are inclined to over-treat, both in terms of starting medication and the doses that they use. I tend to feel it's our condition. I think we're the best people to look after rheumatoid and we should be the ones who do use it [biologicals]." (rheumatologist)*

A view was put that biological treatments should be initiated by rheumatologists as it is currently, but patients could be monitored by general practitioners. This was proposed in relation to a concern for patients located in rural or remote areas where access to rheumatologists might be problematic. Involving general practitioners in such an approach could potentially reduce the problem of access to rheumatological services.

PBS criteria defining who could gain access should, in the view of the vast majority of participants, be under regular review – another major theme emerged (see Section 3.6.2.5).

3.6.2.1.2 Individual care versus public good

One point of divergence between stakeholders was the balance between meeting individuals' and the society's needs. The challenging tension between individual care and community-wide needs was acknowledged by all participants. Overall, government advisors and public servants had common public good as higher priority than individual patient care whereas the other stakeholder groups (i.e. rheumatologists, patients, consumer representatives, and industry spokespersons) felt that there is a need for this tension to be better managed.

Government advisors and public servants believed in following the utilitarian principle of achieving "benefit in the best way for the greatest number of people".

> "It [controlled access] is entirely defensible in terms of a population utility concept. It's very difficult at an individual patient level." (government advisor)

In the view of government advisors and public servants, the clinical freedom of clinicians was legitimately constrained within the boundaries set by the system for public good as the PBS aims to provide access to medicines across all medical areas:

> "…we have a system that has certain constraints, within that system, within those system constraints, as health professionals we've got to try and do the best thing for the patient in front of us in the context of the Australian system,

and that involves considering some of the system-wide issues" (government

advisor)

Government advisors proposed that open discussion about PBS decisions would enhance community understanding of pressures on the PBS and inevitable constraints on individuals for the interests of the whole population.

"…in the construct of a limited expenditure availability, there will always be

boundaries placed around these sorts of decisions. No matter what decision

you make there will be out-lies who are just beyond the boundaries of your

decision. So I think what we have to do is try and explain that." (government

advisor)

The specificity of the PBS access criteria designed to control access in order to achieve public good makes individual care challenging in the views of the other four stakeholder groups. While monitoring patient responses to biologicals to assess eligibility for continued supply was supported in principle because it ensures that public money is wisely spent, patients were apprehensive that an effective treatment might be withdrawn if one just failed to satisfy the criteria required for ongoing access. Further, it was felt that prescribers might feel pressured to exaggerate or 'fudge' measurements of disease activity to benefit some patients not quite fulfilling access criteria. Such practices would be on the one hand illegal and on the other, unfair to those abiding by the rules and more broadly to the opportunity costs of access to other healthcare across the health system. Some proposed increased flexibility with respect to the timing of the follow-up assessments, including less frequent assessment.

"I think a system that had more flexibility for the renewal, possibly by making the reapplication less frequent, or possibly by having a larger window within which the appropriate blood test could be acquired, or possibly by allowing so-called unacceptably high ESR [erythrocyte sedimentation rate] or CRP [C-reactive protein] or joint count for a period of time, until things settle down again… a little less anxiety-provoking for the patients would be good."
(rheumatologist)

"… it [eligibility for access] should ultimately be the rheumatologist's decision. It shouldn't be anybody else's decision. I mean that's ridiculous. I found that really annoying." *(patient)*

Government advisors and public servants had a different view. They believed that the interpretation of joint tenderness and swelling by clinicians and patients, being subjective, allowed some flexibility (in effect accepting some level of 'fudging') for the health benefits of individuals. Further, they believed that assessment of eligibility was 'flexible' because applications for subsidised treatment were assessed by pharmacists and medical advisors with clinical knowledge from Medicare Australia, the responsible agency. In contrast, patient eligibility for standard 'authority required' PBS medicines (i.e. non Highly Specialised Drugs) is assessed by administrative officers without clinical knowledge who follow a set format of "Question and Answer". Moreover, there were also some interactions between the pharmacists/medical advisors of Medicare Australia and individual rheumatologists to clarify details of patient eligibility for access to the biologicals. For example, when a laboratory test failed to demonstrate high concentrations of inflammatory markers – erythrocyte sedimentation rate or C-reactive protein – because the patient had used

corticosteroid therapies, some patients were still considered eligible for PBS-subsidised biologicals.

However, both prescribers and patients believed that clinicians who see individual patients should have greater discretion to prescribe based on an individual patient's needs because, as a patient put it:

"people in government aren't educated about the disease [RA]".

Clinicians' and patients' desire for the system to be flexible enough to allow exceptions for individual patients was evident. Government advisors and public servants also recognised this demand or desire, but the logistics of how flexibility could be introduced into the system is clearly very challenging. A government advisor expressed the difficulty of allowing flexibility with borderline cases ("grey zones") because of potential financial risk and voiced the opposing view:

"…in principle, that [clinical discretion] would be nice, except it's hard to implement and I think grey slowly melts into blue and then goes into green and yellow and in the end everyone's sort of special… the problem with the high-cost drugs is it's very difficult to be flexible because small changes in flexibility start to blow budgets out to massive amounts of money and that means that the whole principle of equity and equitable access to these things are not obeyed. … I don't think the uncertainty can be borne only by Australian taxpayers."

Having inputs from stakeholders during the development of access criteria was considered as a means to incorporate some flexibility and clinical discretion, in particular, when evidence supporting access for a smaller sub-set or group of patients is minimal, for example, children.

"There's certainly always an exception to every rule… it is very difficult and trials aren't going to be done in every single population and I guess around those grey zones, where there might be handfuls of patients, that you will never get data on, you do need some input in it for some clinical discretion so maybe that's a good job for the rheumatologists who have familiarity with the disease and maybe the patient groups at that point to think about are those circumstances really special or are they just being boxed off as special when they're not really a special group of patients at all?" (government advisor)

Risk-sharing between the government and the pharmaceutical companies was proposed as an approach to deal with such uncertainty about cost-effectiveness in sub-sets of patients and/or possible excessive prescribing for these groups.

3.6.2.1.3 Timeliness of access to medicines

Some interviewees were concerned that the availability of innovative medicines was considerably delayed in Australia. This was partly due to the registration process often occurring later than in USA or Europe, but more significantly due to the subsequent step of achieving PBS subsidy, including the PBAC review process and post-PBAC recommendation delays, usually due to negotiations about the price of the medicine.

"I think there's some reform still that needs to happen in the structure of the PBAC operations and three meetings a year is clearly not adequate." (industry spokesperson)

Patients saw timely access to effective medicines as a vital determinant of their quality-of-life and wished that this aspect of the PBS could be improved for important new medicines.

"[The process] must be quickened up, and the government has to set money aside for certain things such as this, for medical, not only for arthritis but for all types of medical things because patients can't wait. It can mean the difference between the quality of life and the quantity of life and the quantity is nothing." (patient)

3.6.2.1.4 Patient agreement

A *Patient Acknowledgement Form* is to be signed by patients to acknowledge that PBS-subsidised treatment will only continue if the predetermined response criteria are achieved at 12 weeks (described in Section 2.5). This *Patient Acknowledgement* document was seen as a contract between the patient and the government. It reduced the direct pressure on the individual rheumatologists, and represented an opportunity to increase patient understanding that there were responsibilities and risks to be shared by all parties with respect to the use of high-cost specialised drugs.

"It's [the form] basically putting everyone on notice that it [access] is not normal. You would normally just rely on the profession to understand and then orient everyone, you know… That's quite new for drugs which have

already made it into the PBS. I think it was a good idea." (government advisor)

"One of the key issues is the patient agreement, we suggested it to them [PBAC], I think it's a key issue because we could see the situation where there would be a huge amount of pressure on the individual rheumatologist, with the patient sitting in front of them, to keep the patient on treatment and by doing it as a sort of a third party effect with the agreement process, what that really meant was that the patient signed a contract which meant they agreed to discontinue if they didn't meet the criteria. It took it out of the rheumatologist's court, because the rheumatologist doesn't really have to carry the can… if it weren't in place the pressure would have been phenomenal." (rheumatologist)

For patients who did not achieve a sufficient response to meet the PBS criteria for continued access and who, therefore, no longer could receive the drug, clear explanation by rheumatologists was considered to be very important. However, some rheumatologists and patients saw this agreement as "pointless" because treatment would be discontinued even if the patients disagreed, and it was unlikely that patients would wish to continue if the treatment was ineffective. A common view of patients was:

"when you're desperate you'll sign anything and I think that's really unfair because people don't know how well they're going to respond."

It was proposed also that the agreement form should be translated into the common languages other than English spoken in our multicultural community.

3.6.2.2 Bureaucracy versus care

The majority of participants noted that the access scheme had controlled the usage and expenditure of biologicals effectively. This was seen as a good outcome from a fiscal perspective. However, there was concern by some individuals, namely those from the stakeholder groups of rheumatologists, consumer representatives and the industry, that the use of biologicals was inappropriately low.

> *"It clearly isn't a Celebrex-type blow-out, that's good. I think everyone respects that that's happened and that it's [prescribing] been done responsibly." (rheumatologist)*

Most participants, regardless of their stakeholder representation, had the view that medical care had become "more bureaucratic" as a result of the PBS-criteria and the processes to be followed.

> *"It seems to be a very bureaucratic way of giving medical care, rather than a normal doctor-patient relationship… it's eliminating the ability of the doctor to show some level of discretion…" (rheumatologist)*

The majority of interviewees thought the application process was an administrative burden and in part has discouraged some applications, thus in effect, kept the usage down. Public servants agreed it is burdensome but saw this approach as necessary and described it as "up-front compliance".

"… now I know what they [Medicare Australia] will and won't accept most of the time and if you're not even close or if your category is like sero-negative, I'm not going to bother. There's no point. None… I'm not going to waste my time with all that paperwork because I know there's a 100 per cent guaranteed rejection." (rheumatologist)

Some patients felt PBS criteria impeded their access to drugs that they perceived as necessary. Similarly, physicians expressed the opinion that prescribing restrictions prevented some patients from getting the medications they need in a timely manner. In addition, patients were anxious about the coordination of laboratory tests, joint assessments, application forms, and ordering the medicine from pharmacies in order to obtain ongoing supply of the medicine. Some physicians were exasperated by the time dedicated to the paperwork. Physicians experienced difficulties in locating records of laboratory tests and details of treatment history, some of which were held by and dependent upon clinicians who had treated these patients previously. However, improved documentation was seen as a good outcome overall, and an application was easier for newly diagnosed patients.

"I do have a problem with the fact that it is the tightest on earth and it's a pain to go through the hoops and all the paperwork ... I mean I resent that a bit. I've got to spend a lot of time for which I get no money to do it and the frustration and trying to find information… sometimes impossible to retrieve…" (rheumatologist)

Government advisors also recognised the need for making access to HCMs less bureaucratic.

"We need to work to a way that actually allows people to prescribe the drug cost effectively without all these limitations. And that's not easy to do… I think the bureaucratic way is not ideal. It's a first, very rough go at doing something that's really difficult… It's proved to be difficult and it naturally creates an adversarial situation… It's been very difficult to try and feel comfortable about implementing that sort of process again… and I think we need to look at some other ways of doing that… we need to be able to get more people on board to be part of the process to even begin to formulate how else it could operate." (government advisor)

3.6.2.2.1 Impact on the use of resources

Prescribers were uneasy that there was no recompense for the substantial additional time to undertake the tasks required to gain access for their patients. Assistance (e.g. from nurses) was in general unavailable as the majority of rheumatologists in Australia work in private practice (84% (263)) and most did not employ practice nurses. Where nurses were available, considerable workload was imposed on them. A nurse was concerned about the impact that the administrative burden had on hospital resources:

"in some places I think that nurses are doing a lot of the work. And there's nowhere that this has been taken into consideration with staff and issues and so on. It's added at least eight hours a week to my workload."

There was also a resultant increase in the use of other resources. Community nurses or general practitioners were involved in some cases to administer medications because self-injection was relatively new to the majority of patients with

RA and hand function was considerably reduced in severely affected patients. In addition, greater resources were used by the Department of Health and Ageing to organise complex PBS restrictions before they are implemented (pre PBS-listing) and also by the Medicare Australia to administer this complex scheme (post PBS-listing):

> *"A weakness is that it's [the access arrangements] created a great deal of departmental and PBAC activity related to the process of setting up the use of the drug… and more players, and that makes a great deal of work for everybody and you have to really think about the cost effectiveness of that little procedure." (government advisor)*

> *"[Biologicals] are more costly to administer. We've got pharmacists on call and they are paid more than admin staff would be paid. We have to go through a more intensive process in order to approve the application because we lose more money if we approve it wrongly." (public servant)*

3.6.2.2.2 Impact on rheumatology practice

The requirement for an adequate trial of conventional disease-modifying anti-rheumatic drugs (DMARDs) before patients were considered eligible for biological treatment (described in Section 2.5) had promoted re-evaluation of previous treatments and more aggressive use of DMARDs. Some patients most likely benefited clinically from such practices that might not have occurred as comprehensively or in as timely a fashion without the stimulus of seeing whether the patient might fulfil access criteria to a high cost biological medicine. In addition, patients were more readily convinced to go through this imposed schema with the

prospect of access to a biological medicine. In a proportion of patients, resistance to prescription of medicines such as methotrexate or leflunomide occurs because of concerns about the long list of possible adverse reactions. The prospect of gaining access to an effective biological drug might induce a patient to accept prescription of drugs like methotrexate when otherwise they might try to do without it. Quotes below from rheumatologists illustrating these effects.

> *"It's forced our rheumatologists to re-look at the treatment that patients have already received … in reassessing the patient and aiming to meet the PBS-criteria, they actually get their rheumatoid arthritis under control before requiring a biological…"*

> *"It [PBS access criteria for biologicals] has actually made it easier to convince patients to accept more aggressive triple therapy, whereas previously they were very reticent to do so."*

The majority considered that this unforeseen effect of re-evaluating past treatments was beneficial and, in effect, induced a more systematic and comprehensive approach to the treatment of RA nation-wide. However, a concern expressed was that the risk of toxicity may have increased because patients were more likely to be treated with multiple drugs at higher doses.

> *"The criteria of the exposure to DMARDs is also quite restrictive and discriminates against people who simply can't tolerate the medication... DMARDs in combination is perhaps unfair because drugs in combination do increase the risk of adverse effects and you have to balance that."*
> *(rheumatologist)*

3.6.2.3 Partnerships and inclusive decision-making

3.6.2.3.1 Collaboration between stakeholders

There was uniform support for the stakeholder collaboration that contributed to the decision to subsidise biologicals. Further, at the time these interviews were being conducted, there was ongoing discussion between stakeholders, working collaboratively to enable the switching between biologicals under the PBS. However, while government advisors and public servants commented that the representative rheumatologists were cooperative, the companies felt these rheumatologists were less willing to collaborate. Consumers felt that both the specialist group and the government were distant and communication with these two groups was insufficient.

> *"They [Rheumatology Association] never, ever, invited consumers. And it's part of the doctor thing, I try not to mind about it but it does make me angry."* (consumer representative)

Furthermore, some rheumatologists, patients, consumers, and industry spokespersons suggested that consultation among rheumatologists should be wider, that communication could be improved, and that there was room for more openness between key stakeholder representatives and their constituencies.

> *"…it's nice if people in routine clinical practice are also included in this process, because the requirements are actually extraordinarily onerous for somebody who runs a private practice, which by virtue of its nature has a limited timeframe. I think this is one of the issues that gets lost in the translation, that we're not all hospital consultants, [but] we're all subject to*

these regulations. So it's good if there's a broad group involved in the deliberations and decision making." (rheumatologist)

An industry spokesperson commented on the negotiation skills of the representing rheumatologists in comparison to some of other clinical counterparts:

"I don't think they [rheumatologists] had the skills, which is built up over experience, to be able to handle negotiations with government. People like 'gastros' have had good experience over quite a long time with new therapies, and oncologists and cardiologists as well. Rheumatologists are babes in the wood when it comes to dealing with government."

Despite the criticism from consumers, patients, and industry spokespersons about rheumatologists being "over-cautious" and relatively inexperienced in negotiating with the government, an industry spokesperson saw the unique stakeholder consultation as a step forward:

"The TNFs are probably the best example of collaboration, it used to be much worse…"

Stakeholder consultation was a major innovation in the view of all participants regardless of their stakeholder representation and all recommended that it be a part of future processes. Lessons learnt through this experience should be used as the basis for improving this type of process.

"we've learnt something from this and we can build more extensive relationships with the stakeholders… I think going further with the process of engaging with the stakeholder groups so that they understand all the aspects

of this and this becomes part of the overall dialogue of society… and the fact that it's our scheme and we've got to keep it. So I believe that we're on the right track in that way…" (government advisor)

"…the significant benefit from it [stakeholder consultation] is the basis for future development… the understanding, the insights into the process, and the demonstration of the benefits, the possibilities, and the barriers of going through a process like that … there's learning that allows you to actually do it the next time maybe in a better informed way. And the other benefit is that there's a greater awareness of the constraints and the parameters of the process itself by clinicians and other stakeholder groups and probably a greater understanding of the need to approach these things as a win-win, rather than as an adversarial exercise …" (government advisor)

The majority of participants noted that stakeholder consultation needs to be carefully integrated with the complex PBAC process and timeframe:

"I think it's a worthwhile process but you've got to balance that against there being a need to make decisions, there being a very tight timeframe process underpinning the PBAC process itself… These sorts of consultations need to fit into that, otherwise you don't get things done and you start to have other unintended consequences …" (government advisor)

"I think it is good to have other stakeholders involved but you have to be careful that you don't have a committee that's so big that you can't achieve anything" (rheumatologist)

The stakeholder consultation process continued to develop following the initial listing of biologicals for RA. Participation by rheumatologists in the initial stage of the decision-making process was quite limited.

> *"We never really at any stage had the feeling that we were anything other than sort of consultants in the process. It was more that we were involved in the discussion, and they [the PBAC] were pretty much intent on what they were going to do, we had the feeling that there was an agenda but that we were lucky enough to be part of it…" (rheumatologist)*

In subsequent stages communication between the PBAC and rheumatologists increased and became more collaborative.

> *"I think it has been a really happy association. It's been mutually productive. I think it's actually getting better all the time …" (rheumatologist)*

The established "partnership" has enabled more timely PBS subsidy of these biologicals for other important clinical uses in the rheumatic disorders, namely ankylosing spondylitis.

> *"it's a great credit to PBAC that they decided to list infliximab for ankylosing spondylitis on such minimal data. First country in the world allowed infliximab to come up onto a national health scheme for ankylosing spondylitis I think.… so they've listened when we've said there is nothing else that you can use with ankylosing spondylitis. So I think they're [PBAC] prepared to be flexible." (rheumatologist)*

3.6.2.3.2 Stakeholder consultation – who should be the participants?

Some participants believed that there is a limited need for direct consumer inputs because doctors would adequately represent the views of patients, and patients' demand and desire for access to medicines were obvious.

> *"I think there is probably a bit of a limit to the nuts and bolts of the listing in relationship to involving consumer advocacy groups." (rheumatologist)*

Not surprisingly and, in contrast, the majority view was that patients should have a more direct role in the process. The logistical difficulties were acknowledged. Patient representatives would need to be carefully selected and well-informed. Interviewees had mixed opinions about when patients should be involved in the process, but that they should at least be involved in developing the *Patient Acknowledgement Form*, and a patient information sheet that explains the access system, in particular, the possibility of loss of access if response to the therapy is insufficient and criteria for ongoing access are not met.

> *"I don't understand why among the rheumatologists patient-as-advocate is not considered more strongly. So I think there should have been a bit more patient advocacy and I think with the drug companies, they should be looking at the coalface, the rheumatologists that are there every day and talking to the patients and getting their feedback. And it would be really nice if the government did the same thing." (patient)*

Consumer organisations could represent patients in the consultation processes, but qualifications of the staff working in such organisations were thought to be important if they are to contribute to the consultation processes or to produce educational

information. The representativeness of some consumer groups was raised along with a concern that some are funded in part by pharmaceutical companies. It was proposed that this concern may be reduced if conflicts of interest are declared openly.

Some interviewees believed that negotiation between the three primary groups (the PBAC, medical specialists, and companies) was sufficient and would avoid difficulties and lengthy negotiations likely to be associated with wider consultation. However, others proposed that a wide range of stakeholders could provide a more balanced view. For example, general practitioners could provide a broader view of management of patients with chronic diseases.

> *"…we say that we're buying outcomes, well to judge outcomes… it's not just a matter of the specialists' view on that and the GP may understand better what the outcome really has been from a drug… if the patients are actually going back to their GPs for various other reasons related to this medicine… And also what else they're using… the GPs were really left way out of the loop." (government advisor)*

> *"I'm a believer in having a team and being your own sort of team leader and utilising all of the things that you've got, but a lot of information was sent to my GP. My GP and my rheumatologist had a really good rapport and he'd always send letters to her explaining what was on." (patient)*

Other potential stakeholders proposed, depending on the drug and the indication, might include people such as economists, allied health professionals, health services experts, ethicists, and clinical nurses and hospital management if hospital resources were used to implement PBS-criteria.

3.6.2.3.3 Transparency

The majority of interviewees in this study were not directly involved with the PBAC decision-making process or stakeholder negotiations that led to PBS subsidy of biologicals and the establishment of the access scheme. These participants felt unclear about how decisions on the access criteria were made. Greater transparency around deliberations between stakeholders and the rationale behind the selected criteria, currently constrained by confidentiality requirements, was considered essential to enhance understanding of the system, and to enable the PBAC to better defend its decisions and garner broader support. While the PBAC and public servants were constrained by confidentiality requirements, the company making the submission, it was proposed, could provide more detailed clinical and economic information to stakeholders.

> *"We need greater transparency. It's [important] people understanding the system, taking some ownership of the system, involving them through transparency, through education, being prepared to speak to them. The PBAC should defend the decisions. It's all to do with dialogue, with the partnerships. This is not a them-and-us system, this is our system. We all have rights but we all have responsibilities." (government advisor)*

A comment by a rheumatologist summarised the two key elements for future processes: (i) direct consumer participation (see previous Section), and (ii) greater transparency.

> *"I would like to see a more collaborative and more open approach, because I think a lot of the negotiations that eventually resulted in this listing were, whether deliberately or accidentally, shrouded in some secrecy and I know from the PBAC perspective there's been some talk of deliberations being made more transparent. If we were doing this process again and if I had the power to change something, those are the things I would like to see: direct consumer representation and an open and transparent process that we could watch evolving."*

3.6.2.3.4 Communication

Increased communication between stakeholder groups was seen as a major innovation that contributed to the subsequent introduction of the *interchangeability rule*. Administrators and public servants were also more involved in the decision-making process. Communication between public servants and administrators has also increased. Recent establishment of working groups (Highly Specialised Drug Working Groups, at Medicare Australia and at the Department of Health and Ageing), was an important example given by public servants to illustrate the evolving process. More organised involvement of both public servants and administrators is likely to improve efficiency of introducing PBS access criteria and implementing them.

Further improvements in communication and collaboration between companies sponsoring drugs with similar indications would be helpful, particularly because of the complexities of access arrangements, although there are obvious difficulties and

concerns about 'anti-competitive' behaviour to be considered. Interviewees also suggested that communication between stakeholder groups and within the groups needed to be more structured to improve the efficiency of input.

An urgent need recognised by the majority was open discussion engaging the broader community to work out the overarching principles of allocation and access to medicines.

> *"The population as a whole needs to have some debate about where they want to spend their money, they are the ones that are funding it ultimately…"*

Some interviewees pointed out that transparency and information are key pre-requisites for such a discussion.

> *"There needs to be that sort of debate at community-wide level and profession-wide level but that debate can only happen and be properly informed if we've got access to all the information, because those restrictions are based on the information that came through in the submissions."* *(government advisor)*

3.6.2.4 Education

The clinicians at Medicare Australia readily assist with queries regarding applications. However, the majority felt that better provision of information on the criteria and application procedures, particularly in the early stages of implementation, was important. In addition to avoiding confusion and improving efficiency, it would enhance support for the access criteria.

"…clearly there was a very steep learning curve. So everyone, not just the pharmacists there [at Medicare Australia assessing applications] but the doctor at the other end who looked after that [applications]. And they were difficult, those early days because there's this enormous expectation… you learn that it isn't going to be easy, that most people are going to be rejected or won't be eligible. So there was a disappointment phase… and anger after the initial euphoria… it was pretty chaotic all round. Tasmania [Highly Specialised Drug Branch] was then setting up, the rules having only just been agreed to… You'd hope it could have been managed a little bit better."
(rheumatologist)

There was clearly a demand for more information for patients although rheumatologists were generally reliable in providing information on the medicines. Concerns were expressed about the brevity of the written explanation of the PBS restricted access including the potential of withdrawing treatment if response criteria were not met. There was also concern regarding inadequate knowledge about these biologicals among health professionals in general. Clinicians emphasised the importance of providing information on adverse reactions, notably risk of infections. This was potentially a difficult task because some patients feared that treatment might be stopped if they reported infections. Most patients felt that quality-of-life outweighed other considerations including the potential risks of treatment.

The industry interviewees felt that education was a major responsibility of industry, particularly when medicines are subject to complex criteria for access. Rheumatologists agreed that company representatives had been helpful in providing information to them, including PBS prescribing criteria and patient application forms.

'Biologic clinics' had been set up, funded by pharmaceutical companies, to provide assistance to rheumatologists. However, most interviewees expressed a lack of faith in the companies to supply appropriate, balanced materials for patients or the public. Concerns were also raised about fragmented and misleading messages delivered by the media. It was suggested that the government should provide appropriate information to counter the potentially unbalanced influence of industry and media.

A government advisor voiced what information should be provided to empower genuine partnership, while recognising the constraints:

> *"I think information is the answer, information needs to be available, accessible … And then a further step down from accessibility is meaningfulness, and meaningfulness depends very much on individual context… It's [information] meant to provide the link between the PBAC behind closed doors and the practitioner out there feeling like they need information in a timely fashion… But the basis on which a lot of the restrictions are constructed relates to specific information that was contained in the submission, in terms of clinical effectiveness or cost effectiveness, or toxicity, comparative toxicity and therefore communication around those is inhibited."*

Enhanced provision of information on the rationale for restricting access under the PBS – a publicly funded system, how criteria were decided, and the critical difference between "effectiveness" and "cost-effectiveness" of medicines was advocated. This is required to empower those outside the process to understand the rationale behind restricted access. Most participants thought that information provided by the Australian Rheumatology Association (clinical information on the

medicines) and the National Prescribing Service (information about the PBS and its decisions) would be most trustworthy. Consumer organisations were identified as having a role in disseminating information and providing consumer support. Interviewees also suggested that general practitioners and other health professionals, such as pharmacists, could be more involved in educating patients with respect to medicines and PBS access to medicines.

3.6.2.5 Review of access to HCMs

The current system, as described by one interviewee, was more like "a knee jerk" response. The vast majority of interviewees believed that the access criteria should be reviewed regularly and such review should be planned in advance. Drug utilisation data should be analysed, and feedback from stakeholders should be used to refine the access arrangements. The risk-mitigation agreement should also be reviewed. The processes of PBAC decision-making and stakeholder consultation would also benefit from regular evaluation. A public servant also proposed examining the administrative expenses associated with such a scheme:

> "The administration costs [of Medicare Australia] are not a consideration for the PBAC. We need to do some cost-benefit analysis around the cost of building the appropriate systems [of access] and the benefit in reduction of use [of medicines] on PBS."

> "I think it's a good approach for high-cost medicines… limited [access] with careful guidelines but also to constantly review those guidelines with time, and to do it efficiently and rapidly according to need." (rheumatologist)

Although a view was put that issues identified from evaluation would need to be addressed, some of these issues may be unappealing from the government's perspective, thus representing a disincentive for the government to conduct a comprehensive evaluation.

"I think it's [evaluation is] a lovely idea but who's going to pay? The Government wouldn't necessarily see that because it's already purchased. It doesn't necessarily want to know… what would you do if you decide that what you've purchased isn't what you think? Do you delist the drug?" (public servant)

Some were disappointed that a prospective, formal evaluation system of the access scheme had not been established. This was partly because stakeholders could not reach consensus on who should be responsible and appropriate funding sources for such evaluations.

"I don't think there were clear arrangements for the evaluation… because there was never an agreement about who would be responsible for the actual evaluation as a policy initiative in terms of outcomes. We didn't want the company to own the data, like for example as what's happened with thalidomide. They've got no clear objective and the government wasn't picking up the tab… so that issue was never resolved. So that was a weakness, and remains unclear who should be responsible for the actual evaluation of the outcome of this particular policy." (government advisor)

Australian rheumatologists had implemented independently a patient registry to track patient outcomes, and some interviewees suggested that Government and the pharmaceutical industry should fund such a registry collaboratively.

Further, the inadequacy of the current information management system to support a comprehensive effective evaluation was a concern for some interviewees, including public servants who recognised the need for serious attention beyond the current strategy of, in large part, paper-based management of patient applications for Highly Specialised Drugs (including anti-rheumatic biologicals). Information systems would enable better management of access to medicines and monitoring the resultant outcomes for the system as a whole and also for the purpose of internal quality assurance. This was illustrated by the following quotes from public servants:

> *"There has been exponential growth in the drugs that are being administered in this way [controlled access]… for reasons about good governance on information and reliability and recording based on these medications, we should be capturing more information."*

> *"Our [Medicare Australia] Program Review Division certainly has an interest [in the information system]. When they have to do audits of programs they need information on which to base their assessment. The only way they are able to do their audits at the moment is to go to Tasmania and look at the paper and they are quite keen to ensure they have enough information captured in the systems, to allow auditing of the program without having to refer to the paper applications."*

Some rheumatologists and patients considered it a weakness that a review panel for contentious cases, while it had been discussed, had not been established. In contrast, government advisors viewed that, to a degree, special consideration had occurred informally via interactions between Medicare Australia and some rheumatologists. This relates to a sub-theme – 'Individual care versus public good'

discussed previously (Section 3.6.2.1). A patient voiced frustration about the delayed review of the PBS-criteria:

> *"I would like a true appeal system. I would like whoever's in power to try and rectify the situation quickly and that when they put in future criteria for any medicine, that they are very, very careful about the criteria."*

3.7 Discussion

This study employed semi-structured interviews with thematic analysis of the perspectives of relevant stakeholders relating to the development and performance of PBS access arrangements for anti-rheumatic biological medicines in Australia. The major consensus finding was that interviewees acknowledged the access scheme for anti-rheumatic biologicals and increased stakeholder communication to be important developments. Nevertheless, as detailed in this chapter, there were clearly some concerns, but also some constructive ideas for improvement. The findings of this study are useful for informing broader debate on how subsidy systems for high-cost medicines can be strengthened. Evaluation is an important component of the Quality Use of Medicines framework. It is important that outcomes from interventions, namely access scheme for HCMs, should be evaluated to investigate and understand the effects when such interventions are implemented. Stakeholder perceptions accessed using valid methodology is essential for an evaluation of such systems with a view to continued improvement. By including individuals of different stakeholder groups with different and potentially competing interests, this study provides a well-rounded picture of the access scheme and thus enhances the credibility of the findings.

The innovations introduced in establishing the access scheme for HCMs in Australia were considered concordant with the expectation that government is responsible for providing access to effective medicines for patients while using public resources wisely. Limiting access to sub-sets of patients where need has been established and where use is cost-effective was viewed as practical and equitable. The stakeholders were supportive of the proposition that it is possible to make expensive medicines available and affordable for the community and individual patients. That this had been achieved with these drugs was accepted as an important accomplishment. Access to biologicals was necessarily restrictive because of their cost; this was acknowledged by interviewees. Reducing drug prices would obviously allow broader access, but this is unlikely to occur during the patent life of these medicines given the influence of list prices for these medicines achieved in much larger markets than Australia.

It is a challenge to achieve agreement on how "target patient populations" should be defined and what the access criteria should be for any drugs listed on the PBS; the difficulties and complexities are amplified for drugs requiring authority for prescribing. This present study proposes that an open debate about the principles and issues concerned with allocation and access to medicines is needed. This debate has not formally occurred in Australia, and is a critical step towards establishing a sound approach to allocating scarce resources when increasingly effective but expensive drugs are becoming available. A relevant initiative by the National Medicines Policy committees is to integrate "Quality Use of Medicines" principles into future PBS drug review processes.(264) This initiative aims to improve the process of defining the appropriate patient populations where the use of new medicines is cost-effective

and developing systems to better target new medicines to these subgroups of patients in practice. Such an approach if implemented would contribute considerably to improving the system of access to HCMs in Australia.

Criteria for access were seen to be potentially 'unfair' when the rationale and evidence in support of the decision were not publicly available in sufficient detail. For example, the requirement for *rheumatoid-factor-positive-status* to gain access led to much debate and concern, and was subsequently removed (detailed discussion in Chapter 7).(265, 266) This research supports the view that transparency around the rationale and data underpinning decisions is likely to gain public acceptance of the drug review process; a rigorous drug review process is critical for the sustainability of a subsidy system such as the PBS.(267) There has been marked increase in transparency of PBAC decisions (Chapter 7). In particular, since the Australia-United States Free Trade Agreement was introduced, summaries of PBAC decisions have been made available to the public ('Public Summary Documents').(85, 268) Increasing transparency also increases accountability of all parties for decisions and performance of the system. These moves towards transparency were supported by the participants.

Transparency also requires disclosure of conflicts of interest from individual participants in the decision-making process. Clearly, interactions between the numerous players potentially influence the decisions made because each group has different responsibilities and interests, as noted in Section 3.2. In particular, the relationships between the industry and other players (such as doctors and consumers) are under increasing scrutiny.(72) Therefore, it is essential that potential conflicts of interest are declared to ensure open and trust-based dialogue between

stakeholders. The Consumers' Health Forum (Australia's national organisation for health consumers) with Medicines Australia (an organisation representing pharmaceutical industry in Australia) have recently published a report to guide interactions between health consumer organisations and the pharmaceutical industry,(269) and is useful for future interactions between stakeholders.

Besides transparency, open dialogue is also critical to build trust.(270) A recurring theme was the importance of stakeholder involvement (including direct patient participation) in the development of access criteria. Ongoing review of stakeholder involvement process and access criteria was also advocated by the interviewees of this research. While issues about PBS subsidy of biologicals and related information were often discussed at rheumatology scientific meetings and through society newsletters, rheumatologists that participated in the study desired wider consultation in order to incorporate relevant issues of concern at the grass-roots level, and more openness. A relevant change was that, as of March 2005, a rheumatologist was appointed as a new member of the PBAC. Although patients were not directly engaged, collaboration and increased communication between stakeholders that started with the decision-making process applied to these biologicals have been crucial steps forward recognised by all participants in this study. This improvement is concordant with the "partnership" concept incorporated in the National Medicines Policy.

The consumer participants identified an increasing need for the voice of patients and the public to be heard at the PBAC level. Patient participants in this study showed little faith in the government's appreciation of the realities of severe RA, although at the time of decision-making, there were rheumatologists who were members of

PBAC sub-committees. Finding better ways of informing and involving the public is another important issue recognised by the participants in this research. Patients are capable of providing objective input about priority setting for HCMs.(255) Involving the public more effectively and centrally in the discussion about distribution of healthcare resources has also been recognised in the literature.(52) Structured stakeholder involvement could strengthen and improve the process, and also enhance public confidence in the quality of decisions around definitions of patient populations eligible for access to HCMs. Individuals who were engaged in stakeholder consultations are accountable to communicate with their constituencies while respecting commercial confidentiality. Greater transparency around stakeholder deliberations is a position supported by all participants in this research. Decision-making process with stakeholder involvement that is open, fair and subject to regular review should be a goal that is pursued nationally.

"Timeliness" of access to innovative medicines via the PBS in Australia, in comparison to comparable countries, was a concern of the majority of participants. There are likely many complex reasons for these delays. Protracted negotiations about access criteria were identified in the present study. The literature suggests that delays may be partly due to the quality of pharmacoeconomic submissions made by the drug industry. An assessment of the submissions found that 67% had major methodological problems: 62% of problems related to the choice of estimates for effectiveness of the evaluated products and 28.5% to methods of modelling and related clinical assumptions.(271) The PBS assessment process allows for identification and correction of pharmacoecomomic analysis problems, but obviously time to achieve subsidy will be lengthened. The post-PBAC process, which is largely haggling over price, may also cause considerable delays. The post-PBAC process has recently been reviewed by the Department of Health and Ageing and Medicines

Australia collaboratively to improve efficiency, effectiveness and transparency of the processes, as well as enhancing timely access to effective medicines.(272) The level of transparency clearly influenced participants' perception of the issue of "timeliness" of access. It should be acknowledged, however, that a definition of "timeliness of access to medicines" by interviewees of the six stakeholder groups was not actively explored in this study. This is an important issue that warrants further investigation.

There is an opportunity cost associated with purchasing particular healthcare 'products', in that resources allocated to one patient will be unavailable within the healthcare system to treat other patients.(273) Therefore, doctors have a double role: (i) as provider of care and thus also as a patient advocate, and (ii) as a societal agent.(274-276) The challenging dual role of doctors was recognised in this study. In the case of access to HCMs for RA, the pressure on prescribers resulting from this dual responsibility has been reduced significantly as the patient eligibility rules are immutable and further, implemented and supervised centrally by Medicare Australia. However, it is recognised by this study that increasing bureaucratic requirements are a threat and impediment to the acceptance and efficient running of such access systems. The administrative burden imposed on prescribers can be a barrier to enrolling deserving patients and a source of increased costs. Increasing administrative tasks as a means to control access to medicines has also been applied in other countries, such as the United States.(133, 161) The impact of this access scheme on the use of hospital and community resources and services was identified in this study and warrants further investigation. Increased accountability of all stakeholders should allow a reduction of the 'bureaucracy' whilst reducing the risk of inappropriate use outside the PBS boundaries.

There was a clear concern for those individual patients on the 'borderline' of satisfying the eligibility criteria (i.e. patients who have severe RA that is not controlled by conventional, available medicines). It has been argued that while doctors are guided by the needs of their patients, in the context of resource allocation decision makers focus on the needs of the population.(277) The participants in this study also presented both of these views: government advisors and public servants remained wary about any usage outside PBS-criteria while repeated reference by the other stakeholder groups (rheumatologists, patients, consumer representatives, and industry spokespersons) for some local flexibility for clinicians. The PBS system of access to medicines needs to deliver a better balance for patients 'on the margins of access' with respect to the tension between overall population benefit and individual care. This tension has been described as rationalism (the individual) versus empiricism (the population).(278) Balancing this tension is challenging as noted, but meeting the needs of both individuals and the society as a whole is a fundamental goal of Australia's National Medicines Policy (Chapter 2). Establishment of a formal appeal mechanism for contentious cases was proposed as a potential solution to better resolve this constant tension. The details of such a process or others were beyond the scope of this study but worthy of examination as a prelude to improving the PBS system.

The "Patient Acknowledgement" procedure provided an opportunity for patient education, an approach that can contribute to a more patient-centred process of healthcare delivery. Involvement of the individual patient in decisions about disease management is consistent with Australia's National Medicine Policy and Quality Use of Medicine framework. Patient education for empowerment (that is, providing

patients with information on benefit and risks of treatment so that they can make informed decisions) is increasingly advocated and has been associated with better satisfaction,(279) concordance with treatment,(280) and improved health outcomes.(281) A previous study has found that unmet need for *therapeutic* information is low in Australia with physicians and pharmacists having an important role in providing patients with medicines information.(282) The present study confirmed that clinicians had been reasonably reliable in providing adequate clinical information to patients. The importance of patient education is emphasised where a 'continuation rule' was applied, as in this example of access to biologicals for RA and other HCMs (as previously described in Section 2.5). The fear patients have that their biological treatment could be withdrawn was identified in this study. It has also been reported in the United Kingdom that some patients may consciously delay seeking medical help against advice because of concern that this situation might provide grounds for withdrawal of access to subsidised treatment.(283) The present research suggests that implications around continuation rules need serious examination.

By solely focusing on patient acknowledgement of the possible withdrawal of biological treatment, the government failed to use this valuable opportunity to educate patients about the PBS system and its constraints. Some interviewees in this study emphasised the need to make a clear distinction between the *effectiveness* and *cost-effectiveness* of medicines when educating patients. Patients' expectations have been reported in the literature as important factors influencing prescribing.(111) This is why it is important to directly involve consumers in decisions around access to medicines. A relevant concern identified by this study is a need for better knowledge about the PBS, how PBAC makes decisions, and the increasing need to control access to medicines, in particular, HCMs, by health

professionals and the community. This gap still needs to be addressed. Empowerment of all stakeholders is essential to minimise power differences and to optimise participation in decision-making processes.(284) Further, general practitioners were identified as potentially important contributors to the success of controlled access schemes. Teamwork between general practitioners and rheumatologists in the management of RA has been advocated by others.(285) General practitioners could provide a broader view of issues and outcomes associated with chronic diseases such as RA, and act as important educators to patients about the PBS system of access to medicines in the view of participants of this study. This research suggests that both direct patient participation and continuing education of all stakeholders about the PBS system is highly likely to gain community acceptance of the necessity of limited access to HCMs. This will promote cost-effective prescribing and use of medicines and ultimately enhance the sustainability of the PBS.

3.7.1 Study limitations

This study has several limitations that need to be acknowledged. Details about industry sponsorship (for research or any other purposes such as conference attendance) received by individual participants were not collected as part of the demographic questionnaire. Literature suggests that industry sponsorship of research is associated with selective publication and publication bias, thereby compromising the quality of the research.(72) Further, there is evidence of a high level of engagement in research between medical specialists and the pharmaceutical industry in Australia,(286) and it is known that promotional and marketing activities affect prescribing practices.(207, 287) Thus, such interactions with the industry have the potential to influence stakeholder perceptions. However,

as noted previously, marked differences were not identified in the views of participants who had held an advisory position with a pharmaceutical company versus those who had not. Comments favouring industry, across individuals of the different stakeholder groups, were not found.

There are three limitations relating to qualitative research in general that may affect the validity and reliability of the research. These limitations relate to: (i) trustworthiness of interview data, (ii) the restricted nature of the population studied, and (iii) the generalisability of qualitative research. These potential limitations are described in this section, however, the potentially negative effects of these limitations on the credibility of the research have all been recognised and minimised using a number of strategies discussed in detail in Section 3.5.6.1.

Firstly, there are several limitations related to the nature of interview data: (i) "bias": the interviewer's knowledge of the study's goals and objectives may have influenced discussion with the participants, namely, interviewer effects,(246) and the subsequent analyses of interview data may have compounded the problem by adding, potentially, another layer of bias, namely, researcher bias;(260) (ii) the "retrospective" nature of some part of the interviews. A part of the data informing this study were based on participants' recollection of past events, namely, their experiences and perceptions on the PBS decision-making process pertaining to the listing of the biologicals; memories of earlier events are potentially distorted by the passage of time; and (iii) the truthfulness of participant responses. Analyses of data were based on the assumption that what participants said was true.

Secondly, a limitation of the study is the restricted nature of the population studied. Participants in this study represented individual discrete examples and did not necessarily constitute a representative sample, as is expected in this methodological approach. The views and experiences of interviewees may not be representative of all stakeholders across Australia, but the themes that emerged are likely to be similarly identified by other groups assembled to discuss this topic. The six main groups of stakeholders of the pharmaceutical sector and most relevant in the context of access to anti-rheumatic biologicals were included in this in-depth qualitative evaluation. However, inclusion of different and/or a greater range of stakeholders involved in the delivery of pharmaceuticals (for example, pharmacists, community/hospital nurses) may have elicited additional findings. Insights into some managerial perspectives were not obtained because administrators at the Highly Specialised Drug Program of Medicare Australia who assessed patient applications for access declined to participate in the study due to concerns about privacy.

Finally, due to the subjective nature of qualitative research and the restricted nature of the study population, the findings cannot be directly generalised to the larger population being studied. Attention to context is important; the evaluative nature of this study may have elicited more criticisms towards the scheme of access to biologicals. Generalising the findings to accessing other HCMs must therefore be tentative. As for the implications arising from this study being ascribed to other medical areas, attention to disease context would be important; for example, comments about surrogate markers in the monitoring of RA cannot be directly transferred to other medical areas such as the treatment of cancer. In summary, while the limitations of this study were recognised, a number of steps to counteract the limitations has been undertaken (Section 3.5.6.1) thereby strengthening the validity and reliability of the research. Notwithstanding these limitations, the findings

provide an in-depth understanding of the perceptions and concerns of a wide range of stakeholders about access to HCMs, specifically anti-rheumatic biologicals, in Australia.

3.8   Conclusion

Australia's Pharmaceutical Benefits Scheme, like systems in other countries, is adapting to changing healthcare needs including access to HCMs. Significant developments have been introduced to maintain the ability to subsidise access to needed, effective and safe medicines at a price individuals and the community can bear in the context of substantive resource constraints. By exploring the perspectives of stakeholders, using the example of the anti-rheumatic biologicals, issues have been identified that will help to guide the development of policy on managing and improving access to HCMs. A publicly funded access scheme that targets subgroup of patients (where cost-effectiveness has been demonstrated) was agreed to be practical and equitable. It is recommended that policy makers dealing with subsidised access to HCMs might focus upon: increasing stakeholder involvement to assist in determining the "target patient populations", increasing transparency and more trust-based communication among a wider range of stakeholders, continuous review of access criteria and the process including resources to run such access schemes, increasing provision of information and education, improving timeliness of access, and allowing some increase in local flexibility for clinicians while reducing bureaucracy. When resources are constrained, restricting access is an inevitable outcome. Different approaches should be explored and carefully examined to identify the most effective, efficient, and ethical access to HCMs under drug subsidy systems. This is in all our interests.

4. ACCESS TO ANTI-RHEUMATIC BIOLOGICAL MEDICINES: AN EVALUATION USING NATIONAL SECONDARY DATA SOURCES

"If you cannot measure it, you cannot improve it" – Lord Kelvin

This chapter examines the challenges of accessing secondary data to examine the impact of the access scheme for anti-rheumatic biologicals under the Pharmaceutical Benefits Scheme in Australia. The problem of accessibility of data needed to examine the health outcomes associated with the use of high-cost medicines was identified as a critical national issue. A routine system for the ongoing examination of post-subsidy experience of medicine use and outcomes is proposed.

4.1 Introduction

Government-subsidised access to effective medicines provided via the Pharmaceutical Benefits Scheme (PBS) is, in effect, "purchasing" realisable and cost-effective health outcomes, a view articulated notably by the current chair of the Pharmaceutical Benefits Advisory Committee (PBAC).(85) The majority of prescription medicine use in Australia is publicly funded via the PBS and the Repatriation Pharmaceutical Benefits Scheme (RPBS) – about 90% of all prescriptions dispensed through community pharmacies.(288, 289) There is an obligation to monitor the outcomes of such a significant investment to determine whether the expected health improvements are actually realised. Monitoring the outcomes of medicine use is a core component of the national Quality Use of Medicines strategy, a pillar of Australia's National Medicines Policy.(116) Examining

the cost-effectiveness of subsidised medicines in practice is also an initiative of the federal government.(290) The Drug Utilisation Sub-Committee (DUSC) advises the PBAC on patterns and changes of drug use associated with subsidy restrictions. However, there is minimal evaluation of health outcomes.

Population-based data can provide valuable information on patterns of drug prescription and use. Estimates of medicine utilisation using prescription claims databases have advantages over those that rely on self-reports of drug consumption.(291, 292) The accuracy of medication data submitted for reimbursement purposes is usually high.(293) Administrative databases are designed to process and pay claims. Despite the inherent limitations of using prescription claims data for research,(294, 295) claims data have been used in many countries for surveillance of prescribing, and for epidemiological and research purposes.(293, 296-299) The Medicare Australia databases on R/PBS prescription claims have been used to define trends in drug use,(300, 301) evaluate interventions such as education related to drug dosing,(302) examine prescribing restriction changes,(303) as well as to provide feedback to general practitioners about their prescribing practices.(304)

4.2   Health outcomes research using secondary databases in Australia

4.2.1 Australian observational databases

The following two sections (Sections 4.2.1 & 4.2.2) discuss the potential of linked data sources to inform evaluation of health outcomes associated with medicine use in Australia.

Ideally for individual-level data analysis, the key data components informing the health outcome evaluation (namely, medicine use, and health outcomes – laboratory tests and health services use) would be linked within and between databases. From 2002, patients for whom each subsidised prescription has been written are identified via their unique Medicare number and their demographics (e.g. age and gender) recorded; previously only information on concessional patients was captured. This change now enables some degree of evaluation of drug utilisation of all individual patients. However, the current situation is that no one data source provides the capacity to examine medicine use over a long period for the total Australian community *and* can differentiate between prescriptions written for rheumatoid arthritis management or other clinical conditions.

Secondary data sources capturing the use of prescription medicines in Australia are summarised in Table 4.1 and include:

- Department of Veterans' Affairs (DVA) database (Table 4.1): Comprehensive and comparable data sets on drug usage, clinical details and health outcomes are held by the DVA for a subgroup of elderly Australians. The DVA pharmaceutical claims database is a unique resource for examining prescribed medicine use in the entitled veterans. DVA beneficiaries account for 10% of Australians aged 65 years and over, and 25% of Australians aged 80 years and over.(305) The RPBS pharmaceutical supply data captures the reimbursement of prescribed medicines used by the majority of DVA beneficiaries that enables longitudinal studies of cohorts of medicine recipients. Linking pharmaceutical data to DVA hospitalisation data will enable investigation of the potential relationships between medicine use and associated health outcomes. The ability

to link de-identified data sets is an encouraging example of what can be achieved.

- National Prescribing Service (NPS) (Table 4.1): NPS is an independent organisation, funded by the Commonwealth government, which provides evidence-based information and services to health professionals and the community about "Quality Use of Medicines".(119) The NPS database contains a subset of prescription medicine data from various sources (such as Medicare Australia, DUSC, Medic-GP, and BEACH) (305) in order to evaluate its programs for improving use of medicines, for example, use of *Helicobacter pylori* eradication medicines.(306)

- IMS Health data (Table 4.1): Details on total wholesale pharmaceutical distribution to pharmacies (includes prescription and non-prescription medicines), hospitals and non-retail markets are contained within the IMS database. However, this data set does not have the capacity to identify how medicines are prescribed or the population to whom they are dispensed and only provides data from participating pharmaceutical companies.(305, 307)

- The Bettering the Evaluation and Care of Health (BEACH), General Practice Research Network (GPRN), and Medic-GP databases (Table 4.1): These are some longitudinal general practice prescribing data sets. These databases record the clinical indication for which a medicine is prescribed, however, there is only a limited number of general practitioners and patients captured by GPRN and Medic-GP.(307) These databases are useful for examining which medicines are used to treat a specific condition in general practice.

- MediConnect data set: This data set is in the process of being established. It is part of the HealthConnect project that aims to advance electronic health records. It is a recent initiative of the Commonwealth government which is endeavouring to align the medical records of medicines across the health system (records from

doctors, pharmacies, and hospitals).(308) However, there are some major hurdles to integrated health data that are yet to be resolved, including technical (such as missing data and coding) and economic issues of information technology, privacy concerns, and the time and commitment by organisations and individuals to record and share the data.(307)

- The DUSC database: This database is the only secondary data source that has the capacity to assess all prescribed medicines dispensed nationally (subsidised and non-subsidised medicines), however, these medicine use data are not linked to the clinical indications. The details of this database are described in Section 4.4 (Table 4.6).

- Medicare Australia (previously the "Health Insurance Commission") database. This government statutory authority that administers the PBS and other health programs nation-wide, collects data on the prescriptions reimbursed under the R/PBS, and medical services delivered by doctors under the Medicare Benefits Scheme (MBS). Both data sets have a common patient identifier (the Medicare number), thus there is potential for individual-level observational studies on the relationships between medicine use and medical services use with the linkage of the data sets. However, Medicare Australia is prevented by law from merging R/PBS and MBS data. Thus a significant opportunity to assess medicine use and associated outcomes is lost without linkage of these data sets. A recent review of the extent to which information from the PBS and Medicare claims databases can be linked (309) is a welcome step towards better monitoring of the use of medicines and informing health policies, as well as identifying possible risks and outcomes resulting from their use. Medicare Australia data captures the majority of prescribed medicines dispensed in Australia, although again medicine use data are not linked to clinical indication. Use of non-subsidised (i.e. private and below co-payment) prescriptions also is not

captured. Medicare Australia data can be stratified by patient and prescriber characteristics such as age, gender and location.(305, 307) The details of Medicare Australia data on prescription claims are described in Section 4.4 (Table 4.6).

Table 4.1 Secondary data sources in Australia (305)

Data Source	Capture	Prescribing Indication	Details
DVA	Medicines subsidised by the RPBS. Linkage is possible between DVA database and the Medical and Allied Health, and Hospitals databases	No	Patient age, sex, postcode. Prescriber age, sex, postcode. Suitable for person-level analysis
National Prescribing Service	Subset of dispensed medicines subsidised by the PBS (data obtained from Medicare Australia or DUSC). No capture of medicines reimbursed by the RPBS, or OTC medicines. Limited information on medicine usage in public hospitals	No	1998-current. Annual data updates. Prescriber postcode & prescriber specialty. Not suitable for person-level analyses
GPRN	Medicines prescribed. Random sample of *Medical Director* users, 150 practices, 320 doctors, 1.3 million patients, 9 million encounters. No capture of medicines dispensed or OTCs unless documented in notes	Yes	1999-current. Daily data updates. Patient age, sex, postcode. Prescriber age, sex, postcode. Suitable for person-level analysis
BEACH	Medicines prescribed. Random selection of approximately 1,000 GPs each year, record details about 100 doctor– patient encounters. A rolling sample & recruit ~3 weeks ahead. Approximately 20 GPs participate each week, 50 weeks a year	Yes	1995, 1998-current. As of 2005, data are received every 3 months. GP age, sex, postcode. Patient: date of birth, sex & postcode. Cross sectional data, ie not suitable for person-level analyses
Medic-GP	Medicines prescribed Sample of 9 practices, 150 doctors, 60,000 patients, 900,000 encounters, 4 states (WA, SA, VIC & ACT)	Yes	1994-2002. Patient age, sex, postcode. Provider location. Suitable for person-level analysis
IMS	Medicines sold. Sales data for pharmaceutical products sold through retail pharmacies, hospitals and non-retail markets. Only data from participating companies are available.	No	1993-current. Postcode of where medicines were distributed to wholesalers. No patient or doctor information available. Not suitable for person-level analysis.

Note:
Details on DUSC and Medicare Australia databases are summarised in Table 4.6.
ACT= Australian Capital Territory; GP= general practitioner; OTC= over-the-counter; PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme; SA= South Australia; VIC= Victoria; WA= Western Australia

4.2.2 Linking data on medicine use and health outcomes

Data linkage involves the amalgamation of records relating to the same individual from different sources, based on there being individual identifying information in each of the databases to be linked.(310, 311) Data linkage is particularly useful in longitudinal studies. It can provide a rich resource for evaluation of health policy development and for clinical and epidemiological research and, thereby, make a major contribution to the understanding of relationships between medicine use and health outcomes.(311, 312)

Unfortunately, the current situation in Australia is that individual-level linkage of data on medicines and health services use is theoretically possible but not feasible at the national level, and is unlikely to be so in the near future. A formal system for the examination of these data is yet to be implemented. While there are clearly technological hurdles to linking medicines and health outcomes data nationally, the major barriers at present include concerns about patient privacy, a lack of political will, and legislative restrictions on access to, and linkage of, the various data collections.(313) Linkage at the national level requires cross-jurisdictional collaboration between the Commonwealth (custodian of R/PBS, MBS and national death data) and all State/Territory governments (the custodians of hospital separation data), and the adoption of the linkage protocols to ensure optimal privacy protection.

4.2.2.1 State-level data linkage

There is the potential to link some of the databases in some States which could provide results generalisable nationally. Developments and successes with state-based data linkage of Commonwealth and state data such as that established in Western Australia (314-316) have been encouraging and may also provide opportunities for linked analyses that can be generalised to the national picture. The Western Australia Data Linkage System, established in 1995, uses computerised probabilistic matching to link seven core data sets (birth registrations, death registrations, hospital morbidity data, mental health records, midwives' notifications, cancer notifications, and electoral registrations) held in Western Australia and covering 1.7 million individuals, with some of the data sets from as early as 1970s.(305, 314) A protocol has been designed to ensure both strong privacy protection and accurate linkage of these data.(316) While there are some known limitations due to weaknesses inherent in administrative data (for example, lack of details on end points needed to evaluate the effects of health services or medicines),(313, 314) data linkage in Western Australia has enabled evaluation of health services and outcomes in areas including cancer care,(317, 318) psychiatry,(319, 320) health effects of air travel,(321) and indigenous health.(322) More recent developments of this system involve linkage of existing state databases with Commonwealth records pertaining to aged care, PBS and MBS claims. These links will enable individual-level studies of medicine use and associated health outcomes. Pilot studies in the area of diabetes have recently been completed and a number of studies are in progress to explore the capacity of linked data on medicine use and health outcomes.(305) If the Western Australian experience and example is extended, then other legitimate research groups can start to undertake important data linkage projects. Other Australian States, including New South Wales,

Queensland and South Australia are currently establishing mechanisms for linkage between State and Commonwealth health data.(323)

4.2.3 Additional data on high-cost medicines

Despite the absence of the ability to link data for medicine and health services use, a promising new opportunity to evaluate individual clinical outcomes via Medicare Australia was presented with the introduction of highly specialised, high-cost medicines (HCMs) to the PBS list of subsidised medicines. As described in Chapter 2, access to HCMs under the PBS is limited to sub-sets of patients who meet criteria for both starting treatment (active severe disease not adequately controlled using existing cheaper treatments) and continuing therapy (substantial clinical improvement). Prescribers must provide documentation to support patients' eligibility. The data submitted by doctors in support of the claim of eligibility of individual patients for initiating or continuing treatment is assessed centrally by Medicare Australia. The PBS restrictions on access to HCMs thus enforce monitoring and documentation of patients' baseline status and clinical outcomes resulting from treatment with HCMs including the biological agents (etanercept, infliximab, adalimumab, and anakinra) for the treatment of rheumatoid arthritis (RA); other examples include imatinib for the treatment of chronic myeloid leukaemia, and infliximab and etanercept for the treatment of ankylosing spondylitis. Data on the use of HCMs managed under the Highly Specialised Drugs Program, previously described in Chapter 2, (e.g. infliximab, imatinib) are also accessible on request through the Pharmaceutical Access and Quality Branch of the Australian Government Department of Health and Ageing.

Examination of utilisation data and outcomes is important for assessing the broader implications of access arrangements for expensive pharmaceuticals under the PBS at multiple levels. At a minimum, intelligent use of this data should lead to program and health outcome improvement. An attempt to evaluate the health outcomes of patients treated by biologicals using this new opportunity is discussed in Section 4.3.

4.2.4 Registers relevant to the current investigation

This section discusses two national registers relevant to the current investigation of outcomes with the use of high-cost anti-rheumatic biologicals. These registers are: (i) the Australian Rheumatology Association Database, and (ii) Adverse Drug Reactions Reporting system within the Therapeutic Goods Administration of Australia.

4.2.4.1   Australian Rheumatology Association Database

A voluntary database (the Australian Rheumatology Association database, ARAD) to track patient outcomes associated with the use of anti-rheumatic medicines (with a special focus on biologicals) has been established by the Australian Rheumatology Association. Collaboration with the Australian Rheumatology Association was proposed by the investigators in 2003, however, during the early stages of developing this database, research proposals were not accepted. Summary reports were accessible on request.

By October 2005, there was a total of 843 patients enrolled in this database. This included 78 on infliximab, 307 on etanercept, 174 on adalimumab and 3 on anakinra. Of those enrolled, a number of patients (n=140) had discontinued one or more

biological medicines. The top three reasons for discontinuation reported were: 'drugs didn't work' (31%), 'side effect' (38%), and 'failed PBS criteria' (10%). The majority of patients were taking more than one disease-modifying anti-rheumatic drug (DMARD) in addition to their biological therapy. The proportion of patients taking additional DMARDs remained fairly constant over the 12-month follow-up. Changes in doses have not been analysed.(324) Examination of humanistic outcomes (e.g. health related quality of life) is possible with ARAD as enrolled patients are required to complete such questionnaires regularly. However, only about 30% of patients treated with biologicals are registered on this database. This relatively low rate of enrolment may reflect the additional administrative burden on practitioners, and some patients have privacy concerns as well as finding that completing the regular questionnaires is a burden. This emphasises the need for public discussion to address concerns about privacy and to highlight the value of health outcomes research.

4.2.4.2 Adverse Drug Reaction Reporting

Data on the frequency of adverse events come predominantly from four sources: follow-up of subjects recruited to clinical trials, surveillance of patients treated in routine practice (for example, ARAD), observational studies, and spontaneous reporting to national pharmacovigilance systems. Many countries maintain a register of reports of adverse reactions to drugs. Post-marketing surveillance requires co-operation of all parties, e.g. pharmaceutical industry, regulatory authorities, clinicians, and in some countries, patients, preferably at an international level. In the early years of marketing of new medicines, international experience is reviewed annually because of the requirement that the sponsor provide Periodic Safety Update Reports. The World Health Organisation's voluntary reporting system includes cases reported to the national Adverse Drug Reaction Reporting systems

of more than 70 countries, and is capable of generating appropriate and timely alerts.(313)

In general, the spontaneous reporting approach has the advantage of covering a nation-wide population, there are multiple reporting routes (suspected adverse reactions data are collected on a voluntary basis with reports submitted by medical practitioners, pharmacists, dentists, patients, and pharmaceutical industry), and it is useful for detecting unusual or rare events.(325) However, data may be influenced by unrecognised biases. Some influencing factors include: extent of drug use, status of the drug, severity of reaction, and prior knowledge of the drug. Substantial under-reporting to national spontaneous reporting systems has been noted.(326) Other disadvantages include: incomplete and missing data, recall bias, errors in prescription records, and differential bias in reporting adverse drug reactions for various age-gender groups. Furthermore, in the absence of a comparison group, oftentimes it is not possible to distinguish between the influence of the drugs and the influence of the indications for their use.(327)

Australia relies on a voluntary surveillance reporting system, administered by the Adverse Drug Reaction Unit within the Therapeutic Goods Administration (TGA). This Unit monitors the reporting of suspected adverse reactions to medicines in Australia, and these reports are reviewed by medical professionals who are members of the Adverse Drug Reactions Advisory Committee (ADRAC). The Australian reporting system for adverse drug reactions has been acknowledged as one of the best in the world; about half of the reports are submitted voluntarily by health professionals.(328) As in most developed countries, pharmaceutical sponsors have pharmacovigilance responsibility for their registered medicines.(329) A

cumulative summary of reports on suspected adverse reactions for a medicine are readily available on request from ADRAC. However, the adverse events data for drugs, including biologicals obtained from ADRAC cannot be compared directly with the data from other studies or registers. The incidence of events cannot be reliably calculated based on data gathered from a spontaneous reporting system, and there may be unrecognised influencing factors to allow a conclusion of causality with respect to a particular drug. The clinical status, the number and types of medicines that the patients were receiving, and the final outcome of adverse events are often not reported, nor linked to administrative data sets where some clinical and economic information at individual-level could be obtained. Therefore, definitive conclusions about the significance of the reported events cannot be drawn. These systems remain very much alerting mechanisms for possible adverse drug reactions.

Prescription databases are valuable sources for drug surveillance and pharmacovigilance purposes.(330) There is a potential for the Medicare Australia database to be used as an information source for surveillance of adverse drug events now that a unique identifier for all patients (i.e. Medicare number) is included in the database. Use of all available information, that is, worldwide information from pre- and post-market trials, voluntary adverse drug reactions reporting *plus* findings from regular, systematic and ongoing evaluation using linked observational data,(313) is urgently needed to serve the intersecting interests of patients, clinicians, sponsors, and regulatory authorities.

4.3   Health outcome data on high cost medicines: Opportunity lost

In addition to standard records of prescription claims, Medicare Australia collects information on the clinical status of each patient that is required as part of an application for initial and on-going supply of biologicals (Table 4.2), as noted in Section 4.2.3. Such individual-level clinical information at 'baseline' and follow-up is useful for evaluating the long-term efficacy and safety of the medicines as well as determining the effectiveness, utility and appropriateness of PBS controlled access schemes. This section describes an attempt to examine the PBS access scheme for anti-rheumatic biologicals in Australia with respect to patient outcomes using national administrative data sets. The problem of accessibility of data needed to examine the clinical outcomes in relationship to the use of HCMs has been published as a commentary ("*Accessing health outcome data on high cost medicines in Australia*". Med J Aust 2006; 184:411-413).

Table 4.2 Information on individuals collected by Medicare Australia needed for supply of biologicals for the treatment of RA

For initiating biological therapy
- Patient's Medicare number, name, and dates of previous biological treatment
- History of trialed DMARDs (name, dosage, duration, reasons for treatment withdrawal)
- Levels of inflammatory markers: ESR and/or CRP
- "Active joint" counts (any joints that are swollen and tender are indicated on a diagram)

For continuing biological therapy
- Patient's Medicare number, name, and dates of previous biological treatment
- Baseline and current levels of inflammatory markers: ESR and/or CRP
- Reduction of "active joint" count (any joints still swollen and tender are indicated on a diagram)

CRP= C-reactive protein, DMARD= disease modifying anti-rheumatic drugs, ESR= erythrocyte sedimentation rate

The following are examples of questions that could be asked and answered by researchers with access to such information:

- What are the health outcomes (e.g. joint counts, inflammatory markers) of patients who have commenced, continued, switched between, or who have been withdrawn from biological treatments?

- What are the associations between use of biological agents and rheumatoid factor status, disease duration, and conventional antirheumatic drugs usage, and which characteristics are predictive of patient response?

- How many rheumatoid-factor-negative patients have been approved to commence biological treatment since the removal of rheumatoid-factor-positive status as an eligibility criterion?

4.3.1 Aims and objectives

The aim of this study was to examine the controlled access to biologicals under the PBS. The specific objectives were to:

- Investigate the process used to implement PBS criteria
- As far as possible, examine the outcomes of the patients who gained access to biologicals

4.3.2 Methods

Despite numerous Australian studies reporting drug utilisation based on prescription claims,(288, 303, 331, 332) there is limited information in the public domain on the *exact* information being captured in administrative databases. Therefore, a request to access these data was submitted to Medicare Australia based on the information known to be collected in the case of the biologicals for use in RA as part of the

application process for subsidised treatment (Table 4.2). This written request (Appendix 4.1) for administrative data for the period August 2003 to July 2005 was submitted to the Information Services Branch of Medicare Australia in July 2004. Details of this request are described below. Anakinra was not included because it was not PBS-listed at the time of the request. Collaboration with Medicare Australia and/or Department of Health and Ageing on this evaluation was proposed by the investigators but no response was received despite numerous attempts at communication.

4.3.2.1 Details of data request

Information about the application review process for biologicals for the treatment of RA which was requested from Medicare Australia included:

- Monthly number of applications received and approved to commence/continue subsidised treatment with etanercept, infliximab, or adalimumab

- Monthly number of applications received and approved to commence/continue subsidised treatment with etanercept, infliximab, or adalimumab by geographical categories: 1= Capital city, other metro; 2= Large rural, small rural, other rural, and 3= Remote centre, other remote, and unknown.

- Average time interval between application and decision on application

- Reasons for rejection of applications

- Most common issues raised and submitted as enquiries or requiring further correspondence between Medicare Australia personnel and prescribers (top 20)

De-identified individual patient information was also requested from Medicare Australia. Data of interest and requested were based on the known information that must be supplied by prescribers to Medicare Australia. These included:

- Patient demographics (age, gender)

- Other anti-rheumatic drugs individual patients had trialed

- Baseline clinical status (levels of inflammatory markers and joint counts)

- Subsequent clinical outcome at follow-up assessment (concentrations of inflammatory markers and joint counts at subsequent assessments)

- Geographical pattern of usage of biologicals and conventional disease-modifying anti-rheumatic drugs (by Australian States and Territories, and by capital, rural, or remote areas)

A relevant report by the Highly Specialised Drug Branch of Medicare Australia to Department of Health and Ageing on the utilisation of biologicals and other anti-rheumatic drugs was also requested by the investigators.

4.3.3 Results

4.3.3.1 Outcome of data request

Repeated and protracted communications with the Highly Specialised Drug Branch and the Information Services Branch of Medicare Australia took place between July 2004 and July 2005. This data request was approved by the External Requests Evaluation Committee of Medicare Australia. In March 2005, Medicare Australia agreed to release a sub-set of requested information (Table 4.3) with a data recovery charge of A$3775.50. Given that this sub-set of data was not sufficient for the purpose of the study, the data were, therefore, not purchased. The report by the Highly Specialised Drug Branch of Medicare Australia on the utilisation of anti-rheumatic drugs was not released.

Table 4.3 Information Medicare Australia agreed to release

Individual level prescription information:
- Medicine: item code, generic name, brand of item, strength and quantity
- Cost
- Original or repeat prescription
- Date of supply
- Payment category: e.g. general, concession or safety net

Aggregated (on a monthly basis):
- Number of prescriptions by age group
- Number of prescriptions by rural, remote and metropolitan areas
- Number of initiating treatment applications received
- Number of initiating treatment applications approved
- Number of continuing treatment applications received
- Number of continuing treatment applications approved

4.3.3.2 Information available from Medicare Australia databases

This section provides the details of information captured by Medicare Australia databases on "authority-required" prescription medicines that was discovered through this study.

Medicare Australia maintains various electronic databases. A "transactions" database records claims from pharmacies for all subsidised medicines (Table 4.4). Data on utilisation of non-subsidised medicines are not captured in this database. A separate database, the "authorities" database, stores computer records of 'authority prescription' requests (thus including clinical indication) and approvals (Table 4.5); the purpose of this database is to govern payment for supply of medicines for approved 'authority prescriptions'. These data are potentially accessible at both an aggregated and de-identified, individual level including claims on all subsidised prescription medicines as of 2002 (i.e. medicine usage profile).

Table 4.4 Prescription claims data from the "transactions" database held by Medicare Australia

- Pharmacy: ID, location of pharmacy (state, postcode)
- Patient: ID, residential address postcode
- Claim payment category: general, concessional, pensioner, repatriation, doctor's bag, safety net
- Prescriber: ID, postcode for major practice of provider, gender, major specialty
- Date item was prescribed
- Date item was supplied
- Code indicating the type of prescription: original, repeat, authority, authority repeat, DVA authority, DVA authority repeat, deferred supply, dental, doctor's bag
- Manufacturers code
- Therapeutic group code
- Drug: name, dosage, form and strength, drug type (a code indicating the type of drug such as chemotherapy special benefit, doctor's bag, dental, general, human growth hormone, highly specialised drugs, Special Access Scheme, special benefits)
- Cost: amount payable to pharmacy
- Number of repeats
- Number of times this item has been previously supplied on this prescription, including the original
- Authority item code

DVA= Department of Veterans' Affairs, ID= identification number

Table 4.5 Data from the "authorities" database held by Medicare Australia

- Authority ID on prescription form
- Sequence Number of Authority Form
- Patient ID
- Date Authority lodged with Medicare Australia
- PBS or RPBS
- Unique identifier for Prescribers
- Date authority prescribed
- Authority Item Code
- Manufacturers Code
- Authority Application (phone, written, after hours/system unavailable, electronic submitted)
- Authority Reason (authority only drug, increased quantity, increased repeats, increased quantity and repeats, authority only drug with increased quantity, authority only drug with increased repeats, authority only drug with increased quantity and repeats, non authority drug, miscellaneous)
- Authority quantity
- Authority repeat number
- Dosage per day
- Authority dispatch (prescriber, patient, pharmacist)
- Authority assessment result (approved, approved with changes, rejected, pending, previously rejected/now approved, authority not required, cancelled, etc)
- Initials of the officer approving the authority
- State in which the authority was approved
- Approval number for authority
- Date authority approved by Medicare Australia and the authority assessment result recorded
- Whether the original prescription has been supplied
- Unique Pharmacy ID number
- Date that the claim was registered
- Category: general, concessional, pensioner, repatriation, doctor's bag, safety net
- Private Hospital provider number
- Number of days the treatment is supposed to cover
- Date and time of last update/amendment of row
- Identifier and location (by state) of operator who updated/amended row last

ID= identification number, PBS= Pharmaceutical Benefits Scheme, RPBS= Repatriation Benefits Scheme

4.3.3.3 *Individual-level clinical information* not *available*

Invaluable health information on each individual patient which is required as part of a written application for biologicals (Table 4.2) is *not* entered into the electronic databases and was, therefore, inaccessible for legitimate research. Unfortunately, the detailed information on individual clinical status was regarded as merely in support of a patient's eligibility for access to biologicals. The existing administrative

databases are only capable of accommodating the 'standard' information from an authority prescription approved and reimbursed by Medicare Australia (i.e. the information summarised in Table 4.4 & Table 4.5). The value of the additional clinical information was recognised by Medicare Australia, to the extent that some of these data are recorded in Excel spreadsheets manually by staff at the Highly Specialised Drug Branch. However, these data do not comply with Medicare Australia's own validated procedures (that is, the reliability, accuracy, and quality of the data are not controlled and cannot be guaranteed) and are, therefore, not released externally by the Information Services Branch of Medicare Australia.

4.3.4 Discussion

The inaccessibility of available data on the use of anti-rheumatic biological drugs in Australia illustrates a number of important issues relevant to the achievement of the best health outcomes and value for the considerable money spent from the public purse. It is not currently possible to study the application review process that governs the access to biologicals for a subgroup of RA patients. Further, it is not possible to examine the additional individual clinical information collected as part of the access scheme for biologicals. Specifically, to examine the impact of criteria for initial access, for on-going supply via the 'continuation rule', and the rates of change from one biological to another and the result of such switching via the 'interchangeability rule' is challenging. Evaluation based on comprehensive, de-identified, individual data would enable a more detailed examination of the use of HCMs in Australia and clearer conclusions to be reached about the clinical and economic effects of the PBS access scheme for HCMs.

The primary responsibility of Medicare Australia to deliver government health programs and, in particular, to employ administrative databases designed to process and pay claims is recognised. On the other hand, the potential role of these administrative databases as a major information source to assist the effort to achieve effective health decision-making and system improvement is becoming increasingly apparent.(333) Requests for access to the data for legitimate research can be made, but the process is usually slow and difficult. For example, the process to request data for biologicals was challenging because: (i) it was unclear from the limited information publicly available what exact details of information are being captured by the Medicare Australia databases; and (ii) there was a lack of an explicit, structured process to be followed for requesting data by external researchers. It should be acknowledged, however, that provision of data to external groups or organisations is not part of Medicare Australia's major role.

The limited usefulness of the currently accessible administrative data from Medicare Australia has been discussed previously.(334) Further concern arising from the present study of HCMs is that invaluable health information on each individual patient collected by Medicare Australia (Table 4.2) via paper-based application forms is *not* captured in its electronic databases and is, therefore, inaccessible for research purposes. This information, which is also required by Medicare Australia's Program Review Division for auditing prescribers, is just as difficult for the Division to obtain (a finding of the interview study reported in Chapter 3). In addition, manual data entry into Excel spreadsheets is time-consuming and expensive. Without information systems and the data therein made available to assess outcomes of this access scheme, effective decision-making to optimise patient care and system effectiveness is severely hampered. A commitment to rigorous monitoring and evaluation by way of a system that tracks both individual and population outcomes

would appear to be a sound investment. Such an evaluation system as a general mechanism for collecting high quality data would provide feedback and evidence that could form the basis for interventions to refine the access schemes. Apart from technical obstacles, other major hurdles include privacy concerns, and the time, commitment and resources (financial, human, and organisational) required of Medicare Australia to make available the data in a timely and appropriate fashion. It should be acknowledged, however, that protecting the privacy of personal health information collected through claims for pharmaceutical and medical services is an appropriate responsibility of Medicare Australia.(335) The Commonwealth Department of Health and Ageing, which holds de-identified data from PBS and Medicare claims and is responsible for regular policy and program review, could provide useful feedback to prescribers and patients to enhance patient management.

Allowing sufficient access to information that is already collected on drug use and clinical outcomes should be the basis for improving the quality of the system. A review and enhancement of Medicare Australia databases, with liberalisation of access to administrative data for approved research, is urgently needed for increasing the accountability and efficiency of allocating public resources for pharmaceuticals.

4.4   Population level, aggregated data sources

Comprehensive and comparable data sets on drug usage, clinical details and health outcomes held by the DVA could be used to examine patient outcomes related to taking specific medicines such as the biologicals. However, the uptake of biologicals in this special population is low (Chapter 5), thereby limiting the usefulness of this data set for this drug group. In the absence of linked individual-level data on

medicine use and health outcomes, and also with the limited accessibility of longitudinal unit record data from Medicare Australia, as described previously, currently the only possible reasonable option for analysis of national data to inform the evaluation of the access scheme for biologicals is to use the population level, aggregated data from (i) Medicare Australia website, and (ii) DUSC database (Table 4.6). These data sets provide the monthly number of prescriptions and associated government expenditure, and trend data can be stratified by geographical locations.

Table 4.6 Secondary data sources in Australia relevant for the present research

	Medicare Australia (formerly the Health Insurance Commission)	Drug Utilisation Sub-Committee
Capture	Claims record of all medicines subsidised by the Australian Government (under PBS and RPBS) – prescriptions dispensed in community pharmacies across Australia No capture of non-subsidised medicines (i.e. private or below co-payment), or medicines prescribed in public hospitals	Dispensing record of all medicines subsidised by the Australian Government (under PBS and RPBS) & estimates of non-subsidised (private and below co-payment) prescriptions No capture of medicines prescribed in public hospitals
Period	Data are retained for up to 5 years only, updated daily.	Data from 1990 to current. The Department of Health and Ageing hold data beyond 5 years Daily data updates from Medicare Australia Monthly data updates from the Pharmacy Guild (survey data)
Prescribing Indication	No	No
Details	Monthly prescription numbers Geographical location (states/territories) Cost reimbursed by PBS/RPBS Patient category (general, concessional, safety net, repatriation)	Monthly prescription numbers Geographical location: stratified by rural, remote, metropolitan areas; or by Divisions of General Practice Cost reimbursed by PBS/RPBS Patient age & sex summary files Patient and prescriber details not available for survey data – therefore not suitable for individual-level analysis
Access Methods	Medicare Australia's web-site, public access with no special permission required	Ad hoc data request
Ethical Issues	Online data is in aggregate form so no ethical issues	Data supplied in aggregate form rather than unit record data so no major ethical issues.
Cost	No charge for PBS online	Free of charge

PBS= Pharmaceutical Benefits Scheme, RPBS= Repatriation Benefits Scheme

4.4.1 Medicare Australia Data

Medicare Australia reports aggregated data on prescription volume and associated government expenditure via its website (Table 4.6).(336) Medicare Australia data available in the public domain comprise the number of 'services' (number of prescriptions) reimbursed by Medicare Australia under the R/PBS and the government expenditure for these prescriptions. In general, each prescription allows a one-month supply of the medicine. Records are generated when the government contributes to the cost of a pharmaceutical product that has been dispensed (claims data from pharmacies) under the PBS, provided that the item costs more than the general patient co-payment, as well as those dispensed under the RPBS for veterans. The month is determined by the date of the reimbursement for the prescription by Medicare Australia, not the date of the prescription or supply by the pharmacy. Generally there is a one-month lag between the date of supply of the medicine (i.e. date of dispensing) and the date of reimbursement by Medicare Australia since claims for reimbursements are processed monthly from pharmacies to Medicare Australia. These figures may vary due to the variable number of working days in a month. Patients paying privately, or funded by private health insurance, are not captured by the claims data. Usage in public hospitals is not captured; this is separately managed by state governments.

Aggregated prescription volume and expenditure statistics on each PBS item available through Medicare Australia's website are updated monthly and are stratified by either States/Territories, or patient categories e.g. general, concessional (including senior and pensioner concessional), and veterans. While these aggregated data that are readily accessible provide some insight on the uptake of biologicals and prescribing trends (Chapter 5), the proportion of patients that were

approved to continue these medicines cannot be determined. It is also not possible to examine the effects of the "interchangeability rule", which allows eligible patients to switch between different biologicals.

4.4.2 Drug Utilisation Sub-Committee Database

DUSC maintains a database of prescription medicines dispensed to the Australian community (Table 4.6).(288) Usage of medicines in public hospitals is not captured by this database. The DUSC data include records on all subsidised prescriptions processed by Medicare Australia, including the number of prescriptions and their costs. The DUSC data from Medicare Australia is collected daily and reported in monthly aggregates with the prescription as the major unit. The advantage of using the DUSC data over using the prescription reimbursement statistics from Medicare Australia (aggregated data described above) is that the DUSC data also include estimates of the number of non-subsidised (private and below co-payment) prescriptions from an ongoing survey in which a representative sample of community pharmacies (142 pharmacies, based on PBS dispensing volume and geographical location) provides records of all dispensed prescriptions for medicines listed on the R/PBS; costs of non-subsidised prescriptions are not available.(337) Patient age and gender summary files for prescriptions are available. Aggregated prescription data can be stratified by the Rural, Remote and Metropolitan Area classification system (338) – see following – and by prescriber major medical specialty.

4.4.2.1 Rural, Remote and Metropolitan Area (RRMA) classification system

The Rural, Remote and Metropolitan Areas system (RRMA) is a classification system developed in 1994 by the Department of Primary Industries and Energy, and the then Department of Human Services and Health. The system divides the rural, remote and metropolitan areas according to Statistical Local Areas and allocates each Statistical Local Area in Australia to a category based primarily on population numbers and an index of remoteness. The index of remoteness considers the distance to urban centres containing a population of 10,000 persons or more, and population density. Seven categories are included in this classification: 2 metropolitan, 3 rural and 2 remote zones (Table 4.7).(339)

Table 4.7 The Rural, Remote and Metropolitan Areas (RRMA) Classifications

Zone	Classification	Category
Metropolitan	1	Capital Cities
	2	Other metropolitan centres (urban centre population > 100,000)
Rural	3	Large rural centres with population 25,000 - 99,000
	4	Small rural centres with population 10,000 - 24,999
	5	Other rural areas with population < 10,000
Remote	6	Remote centres with population > 5,000
	7	Other remote areas with population < 5,000

In summary, in light of the current situation of poor data availability in Australia, it is only possible to: (i) examine biological use at an aggregated level, and (ii) examine DMARDs use at an aggregated level to assess the impact of availability of biological medicines under the PBS. The next two chapters consist of two phases of this research, each one using a different data source on a national level to answer these different but complementary questions. In addition, due to inadequate data on patient outcomes in Australia, examining the international experience with biological treatments is pertinent, and is discussed in the following section.

4.5 Lessons from the international experience

This section examines the need for ongoing evaluation of drug use, the uncertainties about long-term safety of anti-rheumatic biologicals, and the international experience with biological treatments. The significance of patient registries in complementing evidence from controlled trials is highlighted by examples of registries from the United Kingdom (UK) and Sweden. The success of these patient registries provides important lessons for Australia with respect to post-marketing/post-subsidy evaluation of medicines.

4.5.1 Limitation of evidence from Randomised controlled trials

Long-term safety data are almost certainly lacking at the time of marketing authorisation. Randomised controlled trials (RCTs) represent a design able to assess drug efficacy and to detect common, immediate, and pre-defined adverse effects. In order to increase statistical power and to minimise safety risks, pre-marketing trials are generally conducted in often highly selected patients who are free of co-morbidities. Good or acceptable tolerance in trials does not necessarily mean that the drug will be safe in patients who are treated in everyday practice. In addition, the sample sizes are usually too small and follow-up too short to ensure detection of rare but serious adverse events, an increased rate of serious infections, or longer term effects. This is particularly true as strict inclusion and exclusion criteria (including age and gender) may limit the study to patients at low risk of infection.(340) Thus adverse effects may be detected only after the drug is approved for marketing. Furthermore, data from RCTs may overestimate effectiveness of drugs in the community.(341)

The shortcomings of current post- (and pre-) approval safety surveillance have recently been highlighted by withdrawal from the market of the cyclo-oxygenase-2 inhibitor, rofecoxib (Vioxx®).(342, 343) More comprehensive surveillance of all medicines is increasingly considered as a component of the requirements for post-marketing epidemiological studies by the United States Food and Drugs Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA). There are similar discussions in Australia as the establishment of the combined Australia New Zealand Therapeutic Products Authority is underway.(344) However, regulatory authorities in general do not have the means to conduct studies to confirm longer term safety of drugs. Some regulatory agencies such as the EMEA have demonstrated their ambition to ameliorate the situation by making their decisions conditional on various post-marketing monitoring requirements to compensate for the limited safety and effectiveness information present at the time of approval.(345) This was the case with etanercept, where the approval in the European Union was linked to a requirement for long-term follow-up to monitor safety and results are reported to the drug agencies. Thus, national registers to monitor the long-term safety of anti-rheumatic biologicals have been established in most countries in Europe (further discussed in Section 4.5.3).

Besides drug safety, the "real-world" effectiveness of new drugs, and aspects such as pharmacoeconomics, prescribing patterns, and therapeutic strategies for rational and cost-effective use of drugs cannot fully be assessed using the data from RCTs. Healthcare authorities responsible for reimbursement decisions demand this information but at the time listing and access decisions are made, this type of information is often predicted from pharmacoeconomic modeling analyses.

Therefore, if we wish to gain a true picture of a new drug in routine use, it is evident that after approval for marketing, new drugs must be monitored in the everyday clinical setting. Patients, in practice, need to be monitored for many different and often simultaneously prescribed drugs. Further, comparator groups of patients with similar disease on different (or no) treatments are required in order to enable quantification of the risk of co-morbidities occurring due to the use of a particular drug.

4.5.2 Uncertainties about long-term safety of biologicals

Tumour necrosis factor-alpha (TNF) has a crucial role in the body's defence against both bacterial and viral invasion.(346) Anti-rheumatic biologicals have been extensively studied during the past decade and have demonstrated acceptable profiles of safety and tolerability.(347-351) Nonetheless, safety concerns persist. The majority of RA patients enrolled in clinical trials of biologicals had already experienced treatment failure with multiple DMARDs, and had advanced disease of long duration. These characteristics are associated with an increased risk of co-morbidities such as serious infections,(352) and lymphoma.(353) Further, RA patients are already at an increased risk of serious infections, cardiovascular disease, and autoimmune disease in comparison with age- and gender-matched controls.(352, 354-356)

Reports about the safety of TNF-alpha inhibitors, including a risk of serious and rare infections,(357) congestive heart failure, opportunistic infections, including tuberculosis,(358) multiple sclerosis, demyelinating disorders, systemic lupus erythematosus or lupus-like syndrome, and lymphoma have been accumulating in the literature.(355, 359) However, it is difficult to interpret the importance of these

events due to under-reporting, uncertainty about the actual number of patients treated, and RA patients have an increased risk of infections and other diseases (e.g. cardiovascular disease) as noted above. A recent report claims an increased risk of serious infections and a dose-dependent increased risk of malignancies in patients with RA treated with biological therapies.(233) While some have criticised this report as controversial methodologically and caution was urged in interpreting the results,(360) safety concerns as well as the expanded clinical uses of these drugs (such as in the treatment of psoriatic arthritis and ankylosing spondylitis) emphasise the need for ongoing surveillance.

4.5.3 The significance of patient registries

Carefully conducted large-scale observational studies, or rigorous epidemiological surveillance programs are useful because they provide additional, yet complementary information to that gained from RCTs. The most important confounder when evaluating treatment effects in observational studies is confounding by indication, that is, the risk of an adverse event is not associated with the medicine itself but with the indication for medication use.(361) Another major criticism of observational studies is that unrecognised confounding factors may influence the results.(362) However, recent comparisons of observational studies with RCTs have shown that these studies often produce similar results and that well-designed observational studies do not systematically over-estimate the magnitude of treatment effects and do provide valid additional information.(363, 364)

There are several databases available in the USA to address clinical, regulatory, epidemiological, outcome, and patient care questions for rheumatic diseases.(365-368) National registers have been established by Rheumatology Societies in most

European countries aiming to investigate the long-term safety, effectiveness, and cost-effectiveness of biological therapies in RA. Such countries include the UK,(369-371) Sweden,(372, 373) Spain,(374) Denmark,(375) Switzerland,(376, 377) Norway,(378) Germany,(379, 380) and Finland.(381, 382) Registries were also established by rheumatologists in the UK, Germany, and Austria to monitor the long-term safety and efficacy of etanercept in children.(383) In most cases, a cohort of patients with RA not treated with TNF inhibitors forms a comparison group. These registers have the potential to answer questions about the relative effectiveness and cost-effectiveness of different treatment regimens and patient outcomes, such as reduction in the severity of RA using joint counts and inflammatory markers; frequency of drug side effects; development of co-morbidities, including cardiovascular disease; and overall patient and physician satisfaction. Comprehensive information collected at baseline and follow-up is critical to identify potential confounding variables, i.e. those that have an influence on disease outcome. In general, recruitment into European registers has been more successful (70-90%) than ARAD in Australia as a result of strong support or compulsory requirements to participate by the regulatory agencies. By contrast, in Australia, the TGA, the PBS, as well as the Department of Health have remained generally uninvolved with ARAD to date. A more positive example in Australia is bosentan (Tracleer®) for the treatment of pulmonary hypertension, another "highly specialised drug" subsidised by the PBS as of 2004. The risk-sharing agreement between the Commonwealth government and the sponsor includes a patient registry to examine survival outcome. This registry is funded for three years by the sponsor and managed by an independent party, the Centre of Clinical Research Excellence in Therapeutics at the Monash University.(384) Evaluation of this arrangement and the registry will inform policy development and practice with respect to high-cost medicines.

The experiences in the UK and Sweden provide good examples for Australia to follow, particularly (i) the commitment and support by regulatory authorities to monitor patient outcomes associated with biological treatments, and (ii) comprehensive data sets that is readily available for investigating important clinical and economic questions. These are summarised in the following two sections.

4.5.3.1 United Kingdom

In the UK, the clinical guidelines of the British Society for Rheumatology (BSR) were influential in shaping the guidance by the National Institute for Health and Clinical Excellence (NICE) on prescribing practice with respect to biologicals. NICE, established in 1999 to address local variations in availability of specific healthcare technologies in England and Wales, reviews and provides mandatory 'guidance' on the effectiveness and cost-effectiveness of drugs (and other technologies) which are considered to have a significant impact (e.g. high cost, clinically controversial) on the National Health Service (http://www.nice.org.uk/). The use of infliximab and etanercept for the treatment of severe RA in the National Health Service has been recommended by NICE,(385) and an appraisal on adalimumab is in development.(386) According to NICE guidance, access to biologicals is limited by NICE to a subgroup of patients who must meet starting and continuing criteria (Table 4.8), in general similar to that under the PBS although less restrictive. For example, fewer DMARDs need to be trialed, and less frequent clinical assessments are necessary after the first assessment at 3 months. Access arrangements for biologicals under the PBS, as described in Chapter 2, have been summarised in Table 2.3.

Table 4.8 Criteria for access to biologicals for RA in the UK

Availability	Drugs	Criteria for access
2002	Etanercept Infliximab Adalimumab	• Trialled at least 2 DMARDs (including MTX) for 6 months, plus DAS28 >5.1 • Treatment with TNF inhibitors should be withdrawn if there is an inadequate response (defined as a lack of improvement by at least 1.2 points in the DAS28) at 3 months • DAS28 should be assessed at 6, 12 and 18 months • Patients should be managed by specialist rheumatologists • Sequential use of TNF inhibitors is allowed in the case of toxicity developing to one agent DAS = disease activity scores, based on the swelling and tenderness in 28 joint sites, ESR, plus an overall assessment of disease activity by the patient

DMARDs= disease modifying anti-rheumatic drugs; ESR= erythrocyte sedimentation rate; MTX= methotrexate; TNF= tumour necrosis factor

The Biologics Register is the national registry of patients on biological therapy and was established by the BSR to evaluate the safety of these agents. NICE guidance explicitly recommended that all clinicians prescribing these drugs should register patients with the Biologics Register. As of March 2005, 8,455 patients treated with biologicals and 1,199 patients treated with conventional DMARDs were entered into the British Biologic Register. Such a patient population should have sufficient power to provide some insight into safety of biologicals (including the risk of lymphoma). The register also enables collection of safety data required by the licensing authority.(371)

The collection of individual patient clinical data placed considerable strain on clinical units, and in general there has been a need to increase both the nursing and administrative staff to cope with this additional burden.(370) Administrative tasks may have contributed to a lower than expected registration of patients;(387) about 70-80% of all patients with RA receiving biologicals are on this registry.

Nevertheless, this was a high level of recruitment. The success of the registry is primarily a reflection of a cohesive professional body, and rheumatologists' commitment to and belief in the underlying logic of the Register.(369)

Analyses of data from the British Biologics Register have addressed the following topics: the comparative efficacy of TNF inhibitors as monotherapy, co-therapy with methotrexate, and co-therapy with another DMARD in clinical practice;(388) the clinical factors present at the start of anti-TNF therapy that are associated with response at 6 months in patients with RA;(389) the occurrence of baseline co-morbidity in patients with RA treated with biologicals;(390) the rate of serious infections;(391) and the outcome of pregnancies in patients exposed to biological agents.(392)

4.5.3.2 Sweden

The Swedish social security system covers all prescribed drug costs exceeding SEK 1,800 (approximately A$330) a year to all patients in need, where need is based on their physician's judgement. Thus, the use of biological agents is limited only by drug availability and capacity of the administration facilities. Medical practice is under strong influence of the guidelines from the Swedish Rheumatological Association.(393) The Swedish Rheumatological Association has issued similar guidelines to the BSR but with less rigid emphasis on fulfilling a particular disease activity score. Patients with mild or moderate RA, and those who use systemic glucocorticoid can also be considered for treatment with biological agents.(393)

In Sweden, a number of registries are available for longitudinal observational studies in rheumatic diseases. The potential of registers based on data retrieved from clinical practice, how such data may be linked to national health- and population-registers, and the diversity of clinical issues that may be addressed by these registers has been reviewed.(373)

The Swedish Society of Rheumatology has maintained a nation-wide monitoring registry of RA patients treated by biologicals since 1999. Prescribing of TNF inhibitors was allowed but controlled by the Swedish Medical Products Agency on a named patient basis with compulsory clinical monitoring and reporting before marketing approval in 2000. Various regional registries formed a platform for this national reporting system, which captures about 80% of all patients with RA receiving biologicals. As of December 2005, 7,354 patients treated with biologicals and 5,377 patients treated with conventional DMARDs were included on the national register.(373) Data from the national register may be useful for detecting rarer adverse effects, while the regional registers contain more detailed data. A close collaboration between the rheumatology profession and the Swedish Medical Products Agency, and a coordinated, established professional network already engaged in regular monitoring of treatment and disease activity in patients facilitated this registry, that complements the existing systems of drug surveillance.(394)

In contrast to Australia, the majority of rheumatologists in Sweden work at hospital facilities rather than as private practitioners. Reporting to the register, initially paper-based (data were entered into the database centrally), has been changed to a web-based mechanism that allows data entry and evaluation of patient performance during the patient's visit. Information that is useful in the clinical decision-making

process, such as a graphical and tabular representation of current and past disease activity and medicines, are presented to physicians via the web-based system during reporting. Quality control and assistance with data entry is provided by the register staff. All Swedish residents alive in 1947 or born thereafter have an "individual registration number" (i.e. unique identifier) (395) that is recorded in all medical files, national health- and census-registers (e.g. hospital inpatients and Cancer registers), including the Biologic register. Record linkage of these recorded data-sources can be performed for active monitoring of the outcomes of medicines. Ethical and confidentiality issues have been addressed by the following: access to individual data from these registers is restricted to the physician caring for the individual patient only; the process of data-linkage includes irreversible de-identification of individual data to comply with the relevant legislation; and research using these data sets is subject to scrutiny by an Ethics Review Board.(373) Data-linkage across registers enables comparison of (i) RA patients who have been exposed to biologicals with patients treated with non-biologicals; and (ii) RA patients using non-biological medicines with the general population.

To date, the published Swedish studies have mainly focused on the safety of biologicals. A series of risk assessments regarding malignancies,(396-398) infections,(399) and cardiovascular diseases (400) has been performed, both on a regional level (396, 400) and on a national level.(397-399) Other important questions have also been investigated using data from these registers. For example, costs, benefits, and outcomes of anti-TNF therapies in clinical practice over one-year have been evaluated using the South Swedish register,(401) and a comparison of several response criteria (namely, the American College of Rheumatology [ACR], European League Against Rheumatism [EULAR], and simple disease activity index [SDAI] response criteria) for RA in clinical practice.(402) Etanercept and infliximab

have shown similar efficacy in such longitudinal follow-up studies.(403) Analyses of data from another regional register, the Stockholm register, have examined the issues of switching between biologicals,(404) and dose and frequency escalations with infliximab.(405)

As described above, the success of voluntary national patient registries established to track patient outcomes associated with biological treatments, notably in the UK and Sweden, provides important lessons for Australia with respect to long-term surveillance of drug use and they are encouraging examples of what can be achieved.

4.6   Way forward: A formal post-subsidy evaluation

The risks associated with use of any medicine can never be wholly eliminated, thus post-marketing pharmacovigilance and ongoing re-evaluation are important.(313) Evaluation of drug use and health outcomes can provide important evidence of the effectiveness of medicines, their cost-effectiveness, and the impact of regulatory interventions (such as the PBS restrictions) in the "real world", where many factors affect the outcome other than the medicines themselves. Australia's National Medicines Policy and Quality Use of Medicines frameworks recognise the fundamental role of monitoring and evaluation. Despite this goal, there is limited activity in this realm with the exception of aggregated data. A formal evaluation system of medicine use (post-marketing and) post-subsidy is yet to be implemented for a number of reasons including concerns about patient privacy, a lack of political will, difficulties in accessing administrative data, and restrictions on linkage of the various data sets,(313, 406) as described in Section 4.2. This is a critical shortcoming and discordant with National Medicines Policy. Analyses of

international health outcome data from large observational databases and registries are useful. However, patients treated with biologicals in Australia under the PBS are likely to have more severe disease and be more resistant to preceding drug therapy than patients treated with these medicines in other countries, as a result of our generally more restrictive access criteria. Patients with longer disease duration are at greater risk of treatment-related complications. Therefore, it is important to be able to analyse separately the health outcomes of the Australian patient population.

Observational data on biologicals (and other subsidised prescription medicines) are already available in Australia as a by-product of administrative processes. These data provide a promising resource for monitoring of the safety and efficacy of medicines in the community.(313) Analyses using comprehensive data sets in Australia would provide ongoing evidence of access to medicines, usage patterns, and health and economic outcomes for the PBS. A routine system for the ongoing examination of actual post-subsidy experience of medicine use would seem a wise investment with safety and service optimisation for health outcomes being the motive. Due to concerns about patient privacy and confidentiality (which are valid and appropriate), an opportunity worthy of consideration is to request the consent from patients to access their individual data around HCM provision. This could be achieved as part of the *Patient Acknowledgement Form* used in the process of accessing HCMs. This would be an important step to the establishment of a proactive monitoring system.

In addition, rigorous epidemiological data are needed in Australia to provide the evidence base for evaluation and thereby improvement of access schemes. A review of historical trends of medicines and medical services used by patients and

prediction of the likely level of uptake (estimates on the size of the patient population, usage, and financial implications for the government) should be conducted before important new drugs such as the biologicals are introduced more widely into the community (i.e. made available under the PBS) to enable meaningful evaluation of outcomes.

Investment in infrastructure for database and information systems is an absolute requirement if there is to be monitored and improved access to medicines through the PBS. A high quality information technology, in particular one that can provide timely, accurate data on medicine and service uses by patients, treatment strategies and associated expenditure, would have a significant role in contributing to the effectiveness of the access schemes. Unless it is clear which medicines and services are being used and how they are being used by the enrolled patients, it is difficult to monitor quality of care and ongoing financial viability of the access scheme. The present study has identified information technology system development as a key requisite for effective care coordination and evaluation. Wise use of information technology is a means of improving efficiency and monitoring health outcomes.

In conclusion, nation-wide, external, independent examination of the PBS system of access to high-cost medicines from the perspective of system improvement, clinical outcomes or cost-effectiveness is currently challenging. However, recent work in Western Australia, as noted, has shown the practicality of bringing these data together for active monitoring of the use of new drugs in the real-world and the associated outcomes. Australia is replete with observational healthcare data, including doctor visits, medicine dispensing, hospital admissions, as well as deaths

and various disease registries which are collected in linkable databases.(313) With better access to, and use of, existing data resources, Australia is well placed to support pharmacoepidemiological analysis of these large data sets and provide practice-based evidence to complement the evidence of safety and efficacy from RCTs. A formal evaluation of medicine use post-PBS subsidy is an essential way forward for increasing the accountability and efficiency of allocating public resources for pharmaceuticals. Accurate, comprehensive, and reliable measures of the value of pharmaceutical expenditure and health gains obtained are urgently needed in the interests of optimal health and economic outcomes of all Australians.

5. UTILISATION OF ANTI-RHEUMATIC BIOLOGICAL MEDICINES

This chapter examines the national utilisation of anti-rheumatic biologicals under the Pharmaceutical Benefits Scheme (PBS) using population-level, aggregated claims data. This study emphasises the value that would accrue from availability of more comprehensive, de-identified, individual patient data that would enable more detailed examination of medicine use. These data are available but cannot be easily accessed. It is time to make the data available for approved, ethical research in the interests of better outcomes from medicines supplied under PBS.

5.1 Introduction

The fundamental goal of the Pharmaceutical Benefits Scheme (PBS) is to provide Australians with affordable and equitable access to prescription medicines. Accurate prediction of pharmaceutical expenditure is critical if the PBS is to be sustained and limited resources allocated appropriately. The predicted uptake of the medicine and the financial implications are estimated by sponsoring pharmaceutical companies as part of major submissions to the Pharmaceutical Benefits Advisory Committee (PBAC).(187) Sponsors are required to make estimates for at least the first two years of PBS-subsidy based on the prevalence of the disease (chronic conditions) or the annual incidence (acute conditions) together with the likely market share of the new medicine.(85, 187) Submissions to the PBAC for drug subsidy containing these estimates are bound by the Australian *National Health Act 1953* and data are treated as 'commercial-in-confidence', therefore only limited information is made available to the public.(407)

Approximately 1% of the Australian population has rheumatoid arthritis (RA) (408) (~200,000 Australians), and approximately 4,000 of these patients (i.e. about 2% of RA patients) were expected to meet the proposed criteria for etanercept treatment in the first year of subsidy.(409) In a study involving 606 patients from seven centres and whose aim was to gauge their eligibility for access to etanercept, it was estimated that 7,000 patients (i.e. about 3.5% of RA patients) potentially could be treated in the first year of availability of etanercept.(263) These estimates were substantially below other estimates based on different eligibility criteria conducted in other jurisdictions. For example, it was estimated that about 5-6% of patients with RA would qualify for a tumour necrosis factor (TNF) inhibitor based on the entry criteria for the Anti-tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) or using the British Society of Rheumatology criteria.(410-412)

Estimations by the sponsors on the utilisation and government expenditure on the biologicals have not been released. The maximum cost the Commonwealth government was prepared to spend on biologicals for RA via the PBS was A$140 million per annum ("cap") at the time that PBS-subsidy of etanercept and infliximab was approved (2003).(219) A risk-mitigation arrangement between the Commonwealth government and the respective sponsors established an agreed annual ceiling for government outlays. The sponsor of etanercept agreed to cover any expenditure beyond A$100 million.(219) The 'forecast' on expenditure for the first 12 months of availability of etanercept and infliximab under the PBS in 2003/04 was released on the PBS web-site in June 2004; A$77 million for etanercept, and A$18 million for infliximab.(413) The basis for this forecast was not made available to the public. It was also unclear from documents available in the public domain what alterations were made to the original forecasted expenditure or the 'risk-

mitigation' arrangements as a result of the subsequent PBS-subsidy of adalimumab and anakinra in 2004. Utilisation of biologicals under the Repatriation Pharmaceutical Benefits Scheme (RPBS) was not included explicitly in the projections. The RPBS provides pharmaceutical benefits to veterans and eligible dependants that in general conform to the same requirements as for the PBS. Availability of the four biologicals for the treatment of RA under the PBS is illustrated Figure 5.1.
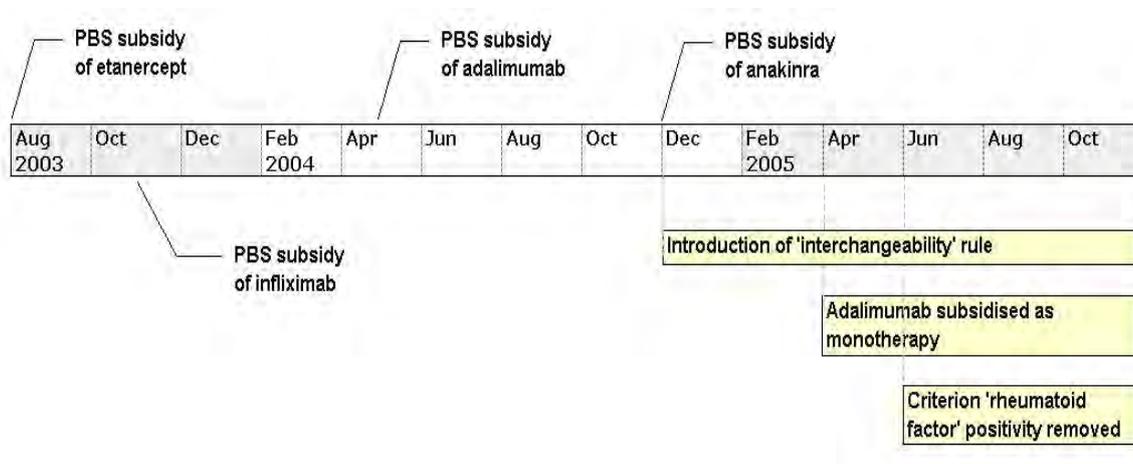
Figure 5.1 Timeline – Access to biologicals for rheumatoid arthritis via the Pharmaceutical Benefits Scheme

5.2   Aims and objectives

The aim of this study was to examine the utilisation of biological drugs for the treatment of RA over the first two years of PBS subsidy (August 2003 to July 2005). The specific objectives were to:

- Analyse separately the uptake of etanercept in the first-year and the associated expenditure under the R/PBS in order to compare these data to those forecasted for the first 12 months of PBS-subsidy

- Examine the uptake of all four biological drugs for RA and the associated expenditure under the R/PBS

- Examine the utilisation of biologicals by geographical location:

    □ States and Territories

    □ Rural, remote, and metropolitan areas

5.3 Methods

A retrospective analysis of aggregated data on the national utilisation and expenditure for etanercept, infliximab, adalimumab, and anakinra in the treatment of RA under the R/PBS was undertaken for the period August 2003 to July 2005.

5.3.1 Medicines of interest

PBS item numbers used for the search and data collection from the Medicare Australia web-site (http://www.medicareaustralia.gov.au/) were:

- Etanercept (25 mg x 8 vials/prescription): 8637N (initial treatment), 8638P (continuing treatment)

- Infliximab (100 mg, quantity supplied on the basis of the weight of the patient, at a dose of 3 mg/kg for a single infusion): 6397Q

- Adalimumab (40 mg x 2 injections): 8737W (initial treatment), 8741C (continuing treatment)

- Anakinra (100 mg x 28 injections): 8773R (initial treatment), 8774T (continuing treatment)

Recommended therapeutic regimens and modes of administration of these biologicals are different. Etanercept, adalimumab, and anakinra are given subcutaneously (25 mg twice a week, 40 mg every 2 weeks, and 100 mg daily,

respectively), while infliximab is administered by intravenous infusion at a recommended starting dose of 3 mg/kg at weeks 0, 2, and 6, and then every 8 weeks thereafter.

5.3.2 Medicare Australia Data

Medicare Australia maintains an electronic claims database for subsidised medicines. Data available from Medicare Australia web-site comprised the number of prescriptions reimbursed by Medicare Australia under the R/PBS and the government expenditure for these prescriptions (described in Section 4.4).

With respect to biologicals, 'initial treatment' includes a prescription for 4 weeks of treatment and 3 repeat prescriptions, for a maximum of 16 weeks of treatment. 'Continuing treatment' comprises a prescription and 5 repeat prescriptions, for a maximum of 24 weeks of treatment. 'Continuing treatment' accommodates prescriptions used by eligible adult patients with RA who:

- were given approval to continue following the first clinical assessment 12 weeks after they started etanercept, adalimumab, or anakinra under the R/PBS
- received a second or subsequent approval to continue access to biological agents, a requirement that needs to be met every 6 months indefinitely.

'Initial treatment' (maximum of 22 weeks) and 'continuing treatment' (maximum of 24 weeks) of infliximab for RA are both recorded under 6397Q.

The aggregated prescription and expenditure data for biologicals was stratified by States/Territories, and by patient categories e.g. general, concessional (including senior and pensioner concessional), and veterans. Although usage in public hospitals is not captured (separately managed by state governments), treatment of RA with biological agents is largely undertaken in ambulatory private practice in Australia; with the exception of infliximab which is supplied through public and private hospitals under the Highly Specialised Drugs Program.(190) Biological prescriptions by rheumatologists in the Northern Territory and in remote areas may be distributed through the Aboriginal and Torres Strait Islander Health Services under Section 100 of the *National Health Act 1953* and these data are not captured by Medicare Australia or DUSC,(414) however, this usage is likely to be very limited due to the small number of rheumatologists in these areas.

Medicare Australia reimburses pharmacies the difference between the patient co-payment and the cost of each prescription. The maximum contribution by the PBS through Medicare Australia for biologicals for the treatment of RA was A$1,888 per prescription. Etanercept, adalimumab and anakinra are available as self-injection formulations; the government contribution of A$1,888 also covers the cost of syringes and related materials (e.g. needles and diluents).

5.3.3 Drug Utilisation Sub-Committee Data

Dispensing data were also obtained from the Drug Utilisation Sub-Committee (DUSC) of the PBAC via a written request (Appendix 5.1) to examine the dispensing trends by geographical location. The aggregated prescription data on biologicals were stratified using the Rural, Remote and Metropolitan Area (RRMA) classification system according to practice location of the prescriber (described in Section 4.4)

(338) and by major medical specialty of the prescriber. Data was supplied for Aug 2003-Jun 2005; anakinra dispensing data were not available from DUSC at the time of this study. Aggregated, monthly expenditure data on conventional disease-modifying anti-rheumatic drugs (DMARDs) were also obtained from DUSC for the study period. Expenditure data on the following DMARDs were included in this study: methotrexate, hydroxychloroquine, penicillamine, sulfasalazine, gold preparations (sodium aurothiomalate and auranofin), and leflunomide.

5.3.4 Data analysis

Prescription data were adjusted, by the author, for State population numbers obtained from the 2003 census data from the Australian Bureau of Statistics.(415) In order to examine any association between access to rheumatologists and the uptake of biologicals, the number of practising rheumatologists in each state was obtained from the Australian Rheumatology Association. Information on the proportion of full-time versus part-time rheumatologists, and whether they worked primarily in private practice or in the public system is not documented by the Association.

Estimates of expenditure on biologicals includes: (i) government expenditure for biological medicines only; i.e. potential resource utilisation related to administering the drugs, for example, involvement of community nurses or general practitioners (a finding of the interview study; Section 3.6.2.2), cannot be estimated using PBS claims data held by Medicare Australia because these services are covered under the Medicare Benefits Scheme. Linkage of data from the PBS with those from the Medicare Benefits Scheme is currently restricted as noted in Chapter 4. Costs of administering infliximab, which is supplied through hospitals under the Highly

Specialised Drugs Program, is not captured by Medicare Australia; and (ii) the patient's contribution – Patient contribution to the cost of the medicines was estimated from prescription numbers multiplied by the patient co-payment for that category (i.e. 'general' or 'concessional').

Prescription data on biologicals by the RRMA classification system were adjusted, by the author, for regional population estimates obtained from the Australian Institute of Health and Welfare.(339)

In using these databases to quantify drug usage, the assumptions were that the number of prescriptions reimbursed is a good proxy for (i) prescribing (i.e. most patients prescribed a biological actually have it dispensed), and (ii) consumption (i.e. adherence with these medicines is likely to be high). These are reasonable assumptions for a chronic debilitating disease like RA, and because of the costs of these medicines, as well as the complex process that prescribers and patients have to experience in order to gain access.

5.4 Results

Examination of the DUSC data revealed that 99% of prescriptions were subsidised by the R/PBS, that is, only 1% of prescriptions were non-subsidised (private prescriptions). The following analysis focuses on those prescriptions subsidised by the R/PBS.

5.4.1 First year utilisation of biologicals

5.4.1.1 Prescriptions of etanercept

To address the first objective of this study, prescription data of etanercept in the first year were examined separately in order to compare the usage with the forecast on its usage as described previously. This section has been published ("*Access to tumour necrosis factor inhibitors for Rheumatoid Arthritis treatment under the Australian Pharmaceutical Benefits Scheme. Are we on target?*" Intern Med J 2006; 36: 19-27)

The total number of prescriptions for initial treatment with etanercept on the PBS from August 2003 to July 2004 was 3,638 (A$6.8 million), and there were 3,810 continuing treatment prescriptions (A$7.2 million). There were 119 prescriptions reimbursed under the RPBS ($A229,000). The number of prescriptions increased steadily. Indeed, there was a peak of 'initial treatment' of etanercept seen at 4 months (December 2003) followed by a decline for the remainder of the year. The number of continuing treatments increased steadily throughout this period (Figure 5.2). The maximum number of prescriptions for etanercept processed in a month (952) occurred in July 2004. One year after etanercept was listed (July 2004), assuming that each prescription was supplied to an individual patient (as an individual could only be on *one* biological treatment), by crude estimation less than 1,000 adult patients were using etanercept under the R/PBS for RA. This represents about 25% of the estimated 4,000 adult patients with RA predicted to be eligible for etanercept in the first year. The expenditure on etanercept under the PBS increased steadily over the first 12 months of availability. The total PBS expenditure on etanercept was just over A$14 million, well below the forecasts; that is, 18% of the

official PBS forecast of A$77 million, or 14% of the predicted annual expenditure of

A$100 million according to the 'risk-mitigation' agreement (Figure 5.3).
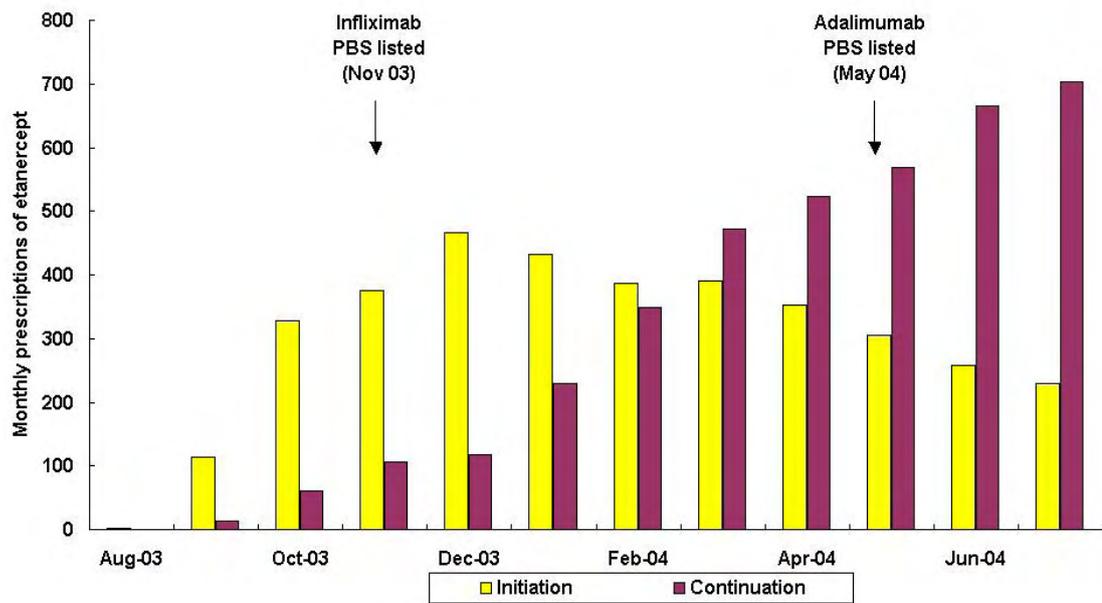
Figure 5.2 Monthly prescriptions for etanercept under the R/PBS, for initiation and continuation of therapy (Aug 2003-Jul 2004)

PBS= Pharmaceutical Benefits Scheme, RPBS= Repatriation Pharmaceutical Benefits Scheme
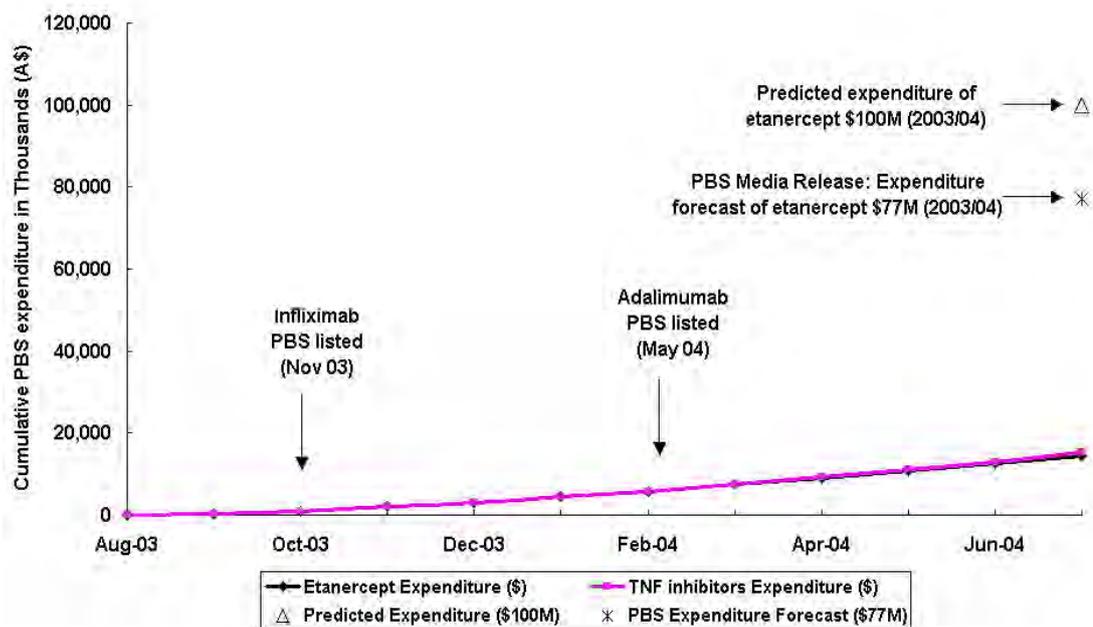
Figure 5.3 Cumulative PBS expenditure on biologicals versus Expenditure Forecast for etanercept (Aug 2003-Jul 2004)

PBS= Pharmaceutical Benefits Scheme, TNF inhibitors = etanercept, infliximab, and adalimumab

Uptake of etanercept was highest in New South Wales with 2,629 prescriptions. However, the relative *per capita* uptake of etanercept indicates that the Australian Capital Territory, Tasmania and South Australia had the highest uptakes (10.5, 9.7 and 7.7 prescriptions per 10,000 population, respectively). South Australia, the Australian Capital Territory and Victoria had the highest *per capita* adjusted number of rheumatologists. The number of etanercept prescriptions was adjusted for State rheumatologist numbers; Tasmania, Australian Capital Territory and South Australia had the highest prescribing rates per rheumatologist (Table 5.1).

Table 5.1 First year utilisation of biologicals for RA under the R/PBS by Australian States and Territories based on aggregate data (Aug 2003-Jul 2004)

	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	TOTAL
Number of prescriptions									
Etanercept	2 629	1 339	851	1 203	752	470	306	17	7 567
Infliximab[a]	44	48	25	26	54	0	0	0	197
Adalimumab	66	44	42	12	27	28	1	0	220
Etanercept Prescriptions per 10,000 population[b]	4.0	2.8	2.2	7.7	3.7	9.7	10.5	1.1	
Number of rheumatologists[c]	85	67	32	28	24	5	5	1	
Rheumatologists per 10,000 population	0.127	0.135	0.083	0.183	0.122	0.104	0.155	0.050	
Etanercept Prescriptions per rheumatologist	30.9	20.0	26.6	43.0	31.3	94.0	61.2	17.0	

Note:
[a] Number of prescriptions of infliximab: usage in public hospitals is not included in the statistical report by Medicare Australia.
[b] Source: Australian Bureau of Statistics, Australian Population – States and Territories, December quarter, 2003.
[c] Number of practising rheumatologists registered as members of the Australian Rheumatology Association
Australian States/Territories: NSW = New South Wales, VIC = Victoria, QLD = Queensland, SA = South Australia, WA = Western Australia, TAS = Tasmania, ACT = Australian Capital Territory, NT = Northern Territory

5.4.1.2 *Prescriptions of infliximab and adalimumab*

Infliximab and adalimumab were both approved for subsidy only in combination with methotrexate for RA. Patients intolerant of methotrexate could be treated with etanercept as monotherapy. Infliximab had accounted for 197 prescriptions (A$453,000) since PBS-subsidy in November 2003 (Table 5.1). Since PBS-subsidy in May 2004, adalimumab had accounted for 220 prescriptions (A$413,000). The requirement that adalimumab be used in combination with methotrexate was removed as of April 2005.

5.4.2 First two years utilisation of biologicals

The utilisation of all four biologicals for the treatment of RA over the first two years of PBS-subsidy was examined to provide the full picture of usage under the R/PBS. The results of this analysis are presented in this section. This section has been published ("*The funding and use of high-cost medicines in Australia: the example of anti-rheumatic biological medicines*". Aus NZ Health Policy 2007: 4:2).

5.4.2.1   *Prescriptions of biologicals and associated expenditure*

There was a total of 27,970 prescriptions reimbursed by Medicare Australia between August 2003 and July 2005 for the biologicals used to treat RA (etanercept, 20,742; infliximab, 851; adalimumab, 6,257; anakinra, 120). The expenditure on biologicals increased steadily over the study period; a total government expenditure of A$53.1 million – 98% by the PBS (A$52 million) and the remainder (A$1.1 million) by the RPBS. The estimated patient contribution was A$267,000 over the study period (0.5% of a total cost of A$53.4 million). Under the PBS, approximately 62% of the prescriptions (17,330 prescriptions) went to concessional patients at a cost of A$34 million, and 36% to general patients at a cost of A$19.1 million. The resultant health outcomes for individual patients are unknown based on aggregated, population-level data (described in Chapter 4).

Reimbursed prescriptions for biologicals doubled in the second year accounting for 71% of total prescriptions over the two years. The government expenditure rose proportionally but was well below the "cap" of A$140 million per annum (19% of predicted). There was only a marginal increase in the number of prescriptions for

'initial treatment' in the second year. The proportion of prescriptions for 'continuing treatment' increased from 50% to 72% of the total prescriptions in year 2 (Figure 5.4). Infliximab was not included in these estimates because prescriptions for this biological were not stratified into 'initiating' and 'continuing' categories.
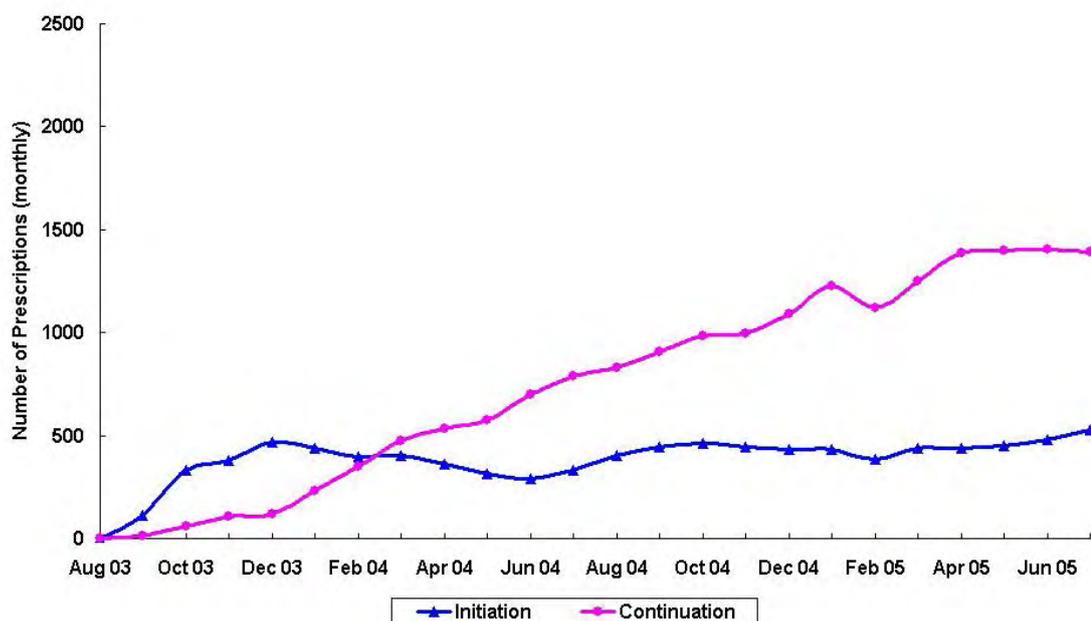
Figure 5.4 Monthly prescriptions for biologicals under the R/PBS, for initiation and continuation of therapy (Aug 2003-Jul 2005)

Note: Biologicals included: etanercept, adalimumab, and anakinra

The maximum number of prescriptions processed in a month occurred in July 2005 – a total of 1,984 prescriptions for the biologicals group (Figure 5.5) at a cost A$3.75 million. Monthly PBS expenditure on anti-rheumatic drugs overall (including both biologicals and DMARDs) has doubled since the biologicals became PBS-subsidised (Figure 5.6); although it should be acknowledged that not all usage of medicines classified as DMARDs is for RA. Assuming that each biological

prescription was supplied to an individual patient, by crude estimation approximately 2,000 patients had commenced biological therapy for RA within the study period based on the aggregated data. This represents about half of the estimated 4,000 adult patients with RA predicted to be eligible for etanercept in the first year. However, it was not possible to determine the proportion of patients that were approved to continue or who were switched between biologicals using the aggregated prescription data, as noted previously.
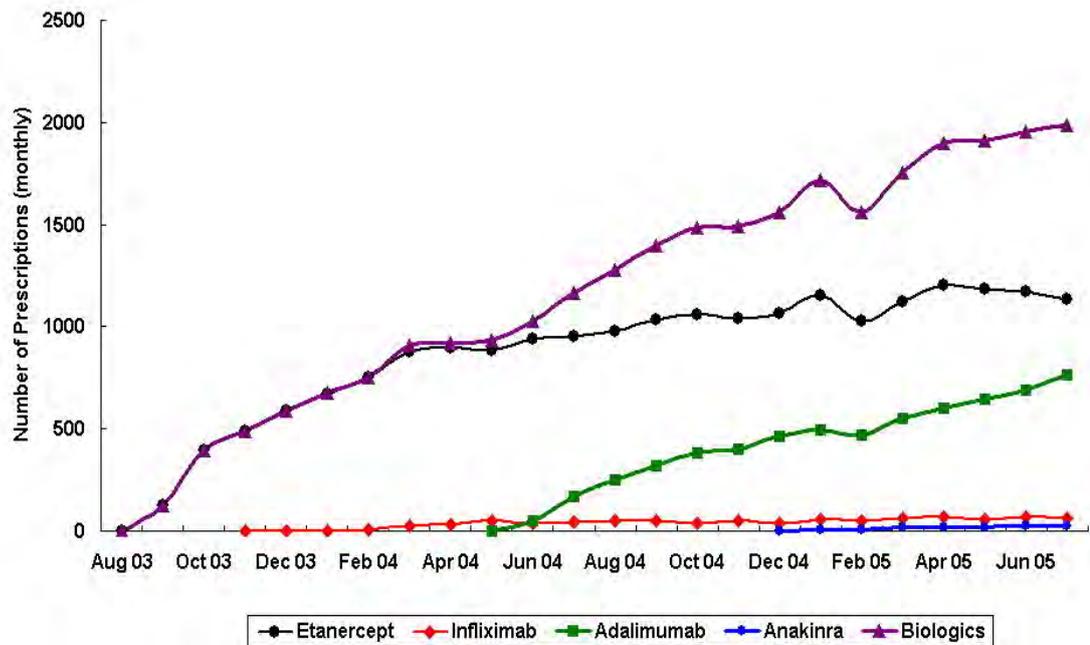
Figure 5.5 Monthly prescriptions for biologicals under the R/PBS, by drug (Aug 2003-Jul 2005)
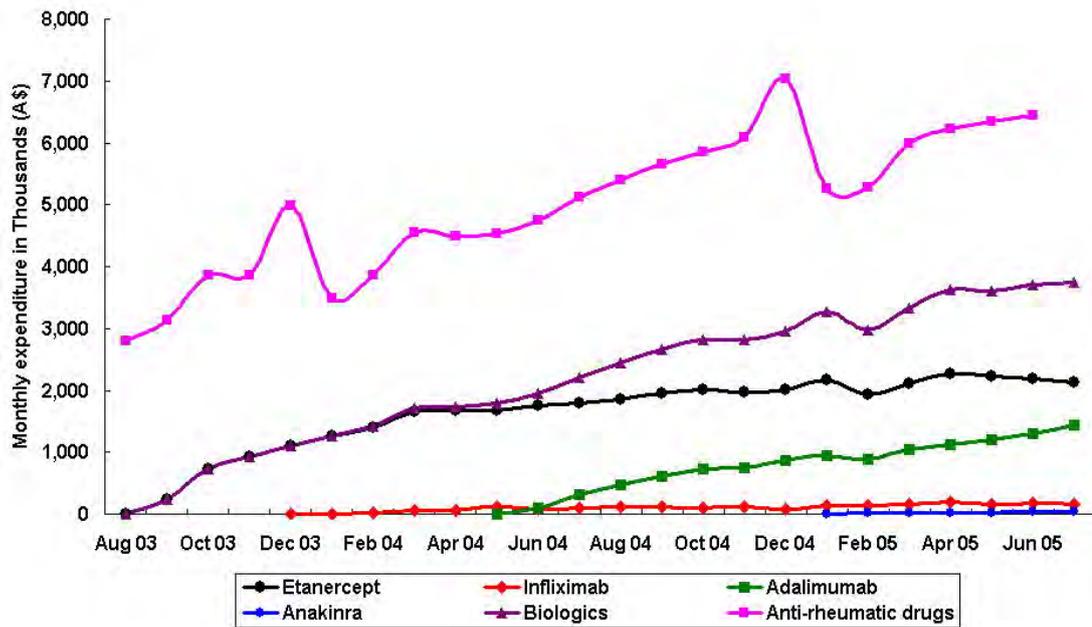
Figure 5.6 Monthly expenditure on anti-rheumatic drugs under the R/PBS (Aug 2003-Jul 2005)

Note: Expenditure on DMARDs was obtained from the DUSC database. DMARDs included: methotrexate, hydroxychloroquine, penicillamine, sulfasalazine, gold preparations (sodium aurothiomalate and auranofin), and leflunomide.

The total number of prescriptions for etanercept under the PBS from August 2003 to July 2005 was 20,398 (A$38.4 million). A further 344 prescriptions (A$647,500) were reimbursed under the RPBS. Initiation of etanercept therapy declined after December 2003. The use of infliximab was considerably lower than etanercept, although infliximab was not PBS-subsidised until November 2003: 826 prescriptions were provided under the PBS (A$2.1 million) and only 25 prescriptions (A$59,000) under the RPBS. Adalimumab was available via the PBS from May 2004. Up to July 2005, adalimumab had accounted for 6,063 prescriptions (A$11.4 million) under the PBS and 194 prescriptions (A$365,800) under the RPBS. Since inclusion on the PBS in December 2004, anakinra had accounted for 115 prescriptions (A$164,000) under the PBS and 5 prescriptions (A$7,100) under the RPBS (Table 5.2).

Table 5.2 Utilisation of biologicals for RA under the R/PBS by Australian States and Territories based on aggregate data (Aug 2003-Jul 2005)

	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	TOTAL
Number of prescriptions									
Etanercept	7 559	3 685	2 205	3 064	2 142	1 085	939	63	20 742
Infliximab[a]	190	182	146	51	280	2	0	0	851
Adalimumab	1 842	1 496	1 096	503	820	369	116	15	6 257
Anakinra	52	17	25	8	17	0	1	0	120
Biologicals Total	9 643	5 380	3 472	3 626	3 259	1 456	1 056	78	27 970
Biologicals Prescriptions per 10,000 population[b]	14.4	10.9	9.0	23.7	6.6	30.3	32.7	3.9	
Number of rheumatologists[c]	86	69	32	29	24	5	5	2	
Rheumatologists per 10,000 population	0.128	0.139	0.083	0.189	0.122	0.104	0.155	0.100	
Biological Prescriptions per rheumatologist	112.1	78.0	108.5	125.0	135.8	291.2	211.2	39.0	

Note:
[a] Number of prescriptions of infliximab: usage in public hospitals is not included in the statistical report by Medicare Australia.
[b] Source: Australian Bureau of Statistics, Australian Population – States and Territories, December quarter, 2003.
[c] Number of practising rheumatologists registered as members of the Australian Rheumatology Association
Australian States/Territories: NSW = New South Wales, VIC = Victoria, QLD = Queensland, SA = South Australia, WA = Western Australia, TAS = Tasmania, ACT = Australian Capital Territory, NT = Northern Territory

5.4.2.2   *Prescriptions of biologicals by Australian States and Territories*

Utilisation of biologicals was highest in New South Wales (7,559 prescriptions). The relative *per capita* uptake demonstrated the same pattern as seen in the first year after listing of etanercept (Section 5.4.1.1). The Australian Capital Territory, Tasmania and South Australia had the highest relative *per capita* use of biologicals (32.7, 30.3 and 23.7 prescriptions per 10,000 population, respectively); initiations and continuations of biological therapies were also highest in these states. The

Northern Territory had the lowest *per capita* use – 3.9 prescriptions per 10,000 population (Table 5.2). There was an 8-fold difference between the jurisdictions for the highest and lowest rates. After adjusting for state population, utilisation of biologicals was relatively low in Western Australia, however, *per capita* use of infliximab was the highest in this State.

South Australia and the Australian Capital Territory had the highest *per capita* adjusted number of rheumatologists, whereas Queensland had the lowest (about 2-fold difference between these two jurisdictions). Prescription rates per rheumatologist were highest in Tasmania and the Australian Capital Territory (291.2 and 211.2 prescriptions per rheumatologist, respectively). The Northern Territory had the lowest prescription rates per rheumatologist, 39 prescriptions per rheumatologist. This also represents about an 8-fold difference between the jurisdictions for the highest and lowest prescription rates by rheumatologist.

5.4.2.3 *Prescriptions of biologicals by rural, remote and metropolitan areas*

Based on the population-adjusted DUSC dispensing data on etanercept, infliximab, and adalimumab, more than half of prescriptions (~60%) were provided by prescribers in the metropolitan areas (capital cities and other metropolitan centres), and a large proportion of prescriptions (27.7%) were provided by prescribers in the large rural centres (Table 5.3). Review by the prescriber major specialty indicated that only a small proportion of prescriptions was provided by immunologists (5.7%), not surprising as most of the prescribing of biologicals for severely-affected patients would be done by rheumatologists.

Table 5.3 Prescriptions of biologicals by Rural, Remote, and Metropolitan Areas (RRMA) classification system based on DUSC data (Aug 2003-Jun 2005)

	Prescriptions per 10,000 population[a]				
RRMA	**Etanercept**	**Infliximab**	**Adalimumab**	**Biologicals Total**	**% of Total**
Capital cities	15.1	0.6	5.2	20.9	30.6
Other metropolitan centres	14.2	0.3	5.5	20.0	29.4
Large rural centres	12.6	1.2	5.1	18.9	27.7
Small rural centres	4.9	0.04	1.3	6.2	9.1
Other rural areas	0.2	0	0.07	0.2	0.3
Remote areas	1.1	0	0.7	1.75	2.6
Other remote areas	0.13	0.05	0	0.25	0.4

[a] Source: Population estimates from Australian Institute of Health and Welfare, based on 2001 census data.(339)

5.5 Discussion

The utilisation and expenditure on biologicals for treating RA under the R/PBS over the first two years was found to be substantially below that forecasted (approximately 19% of the 'cap' by expenditure). Uptake of etanercept was considerably lower than projected (14% by expenditure) in the first year and utilisation did not increase significantly in the second year (Figures 5.5 and 5.6). This is a welcome result from a fiscal perspective in comparison to the experience with the cyclooxygenase-2 inhibitors where usage grossly exceeded forecasts and contributed to an alarming 19% increase in PBS expenditure in 2000/2001.(189) Concerns about inappropriate or over-use of biologicals appear to be unfounded. From this perspective, the PBS restrictions have been effective in governing access and containing government expenditure.

By July 2005, approximately 1% of the RA patient population in Australia had commenced biological therapy. This is substantially lower than that reported in other countries, for example, 14.9% of patients with RA were treated with biologicals in southern Sweden in 2003,(393) and about 20% of patients with RA receive anti-TNF therapy in the United States.(416) However, estimates of patient numbers and associated expenditure on biologicals will vary with the eligibility criteria for the treatment. For example, an approximately 8-fold difference was reported in estimations of patient populations eligible for anti-TNF therapy using different criteria (2% to 15% of 636 patients with RA examined in Norway).(417)

Findings from the qualitative study described in Chapter 3 offer several explanations for the low use of biologicals in Australia: (i) the administrative burden imposed by the PBS restrictions may have discouraged some applications; (ii) there has been cautious selection of patients by rheumatologists because of concerns about drug safety; and (iii) a smaller population of RA patients than predicted achieved the eligibility criteria for initiating biological therapy as a result of the PBS-mandated treatment algorithm (including the use of combination DMARD therapy). Withdrawal from biological therapy may also explain lower prescribing and expenditure than expected. It has been reported that up to 40% of patients do not or only partially respond to biologicals.(418) Finally, it is also likely that the forecasts were inaccurate; data assembled by pharmaceutical companies including the economic analyses have been reported to be error prone.(271) There is no rigorous epidemiological data on most diseases (including RA) in Australia. Such information provides the evidence base for forecasts. Both under- and over-estimates of usage compared with actual usage of other drugs have been reported in two-thirds of submissions for subsidy of medicines made to the PBAC.(134) As of 1 July 2005, some information on the estimation of expected PBS usage and cost to the

government are now published as part of Public Summary Documents regarding the outcomes of PBAC decisions.(268) A recent initiative by the National Medicines Policy committees is to integrate "quality use of medicines" principles into the PBS drug review process,(264) which would help to reduce uncertainty with respect to predictions of usage and outcomes from medicine use. The DUSC, previously responsible for evaluation of drug utilisation post-PBS subsidy only, now has an additional role in assessing the forecasts submitted by sponsors.

Etanercept had the highest usage over the study period. This finding was expected because etanercept was the first agent available under the PBS (August 2003). Further, patients who were intolerant to methotrexate could only be treated with etanercept. Adalimumab was more recently approved as monotherapy in April 2005. The gradual plateau in the utilisation of etanercept (Figure 5.5) probably reflects the introduction of adalimumab under the PBS (Figure 5.1). The steady increase in initiations of adalimumab treatment may reflect the preference for fortnightly administration schedule as compared with etanercept that is administered twice weekly. The considerably lower number of prescriptions of infliximab is possibly due to several reasons: (i) it must be used in combination with methotrexate (in order to reduce the development of human anti-chimeric antibodies and prolong the benefits of the drug (230, 419)), (ii) it is dosed less frequently (administered every 6-8 weeks), (iii) it is administered by infusion but usage in public hospitals is not captured, and (iv) intravenous infusion may be less preferred by prescribers and patients. In particular, dose escalation of infliximab over time, suggestive of acquired drug resistance, has been reported in several studies.(377, 403, 420-422). Further, there have been no head-to-head clinical studies of infliximab, etanercept, and adalimumab in RA, and it is difficult to compare the published data for biological agents from randomised trials because they involve different patient populations,

study designs, and treatment strategies.(423) In the absence of such data, it is unknown whether significant differences exist in their efficacy or safety, therefore preference for etanercept and adalimumab over infliximab is not surprising. The minimal use of anakinra can be explained by its recent listing on the PBS (December 2004) and data that suggest it is less efficacious than TNF inhibitors.(424) The uptake of anakinra over the next few years is not easily predicted because patients who fail to respond to two TNF inhibitors are allowed to trial anakinra (under the PBS 'interchangeability rule').

A small study in Australia demonstrated that etanercept achieved marked clinical improvement in 50 patients who commenced biological treatment under the PBS using various outcome measures including the modified disease activity score response criteria (DAS28), the American College of Rheumatology (ACR) response criteria, and short form questionnaire (SF-36). Out of these patients, 88% continued at 12 months under the PBS access system.(425) As discussed in Chapter 4, such studies are warranted to examine efficacy and tolerance of biologicals in the subgroup of patients who have more severe and resistant RA as targeted by the PBS access criteria. By February 2006, it is estimated that more than 4,000 RA patients had commenced biological therapy under the PBS, and about 65% of RA patients who commenced biological therapy have continued the treatment (personal communication, DUSC). Specific information on continuation rates for each biological agent was not available; difficult access to these data is currently a severe limitation to external, independent research in Australia, as also noted in Chapter 4. This estimated continuation rate is concordant with a German observational study that showed that continuation of biological treatment in clinical practice was lower than in randomised clinical trials. Treatment continuation after 12 months was 69% for etanercept, 65% for infliximab, and 59% for anakinra.(380) In the trials,

continuation of infliximab plus methotrexate was 73%,(426) etanercept alone was 76% and etanercept plus methotrexate was 84%.(427)

The PBS aims to provide equitable access to medicines for the community. However, those with equal needs may not have equal opportunities to access rheumatological services. Prescribing of anti-rheumatic biologicals under the PBS is restricted to rheumatologists and clinical immunologists with expertise in the management of RA. There is a limited number of specialists and reasonable access to a rheumatologist varies considerably between Australian states and territories. Not surprisingly the use of biologicals roughly correlated with the *per capita* adjusted number of rheumatologists (Section 5.4.2.2). Population-adjusted utilisation of biologicals by rural, remote and metropolitan areas also indicated geographical heterogeneity in access to healthcare (Section 5.4.2.3). By comparison, variability in the utilisation of leflunomide (a conventional DMARD specifically used in the treatment of RA) is smaller; prescribing of leflunomide is not restricted to rheumatologists and not regulated by a 'continuation rule'. The accessibility of this drug to general practitioner prescribers is possibly associated with this smaller variation in the uptake of leflunomide across the country (Chapter 6). Other factors potentially influencing the use of specialist care include patient's income, indirect costs (e.g. travel costs, foregone wages), access to information, knowledge, and cultural beliefs.(428)

In addition, there was substantial variability in prescribing rates of biologicals by rheumatologists across the States and Territories (Section 5.4.2.2). It is unclear, however, whether such variability also exists for the prescribing of DMARDs due to the limitations imposed upon analysis when using aggregated prescription data

(Chapter 6). A *post hoc* analysis of demographic data (gender and age) on Australian rheumatologists was conducted by the author to investigate possible reasons for the observed variability in uptake across the country. The majority of rheumatologists were male (71%) and a large proportion of rheumatologists (66%) was within the age range of 40-59 years. This analysis revealed no apparent pattern between the demographic characteristics of rheumatologists and the variability in uptake across the States and Territories. It should be acknowledged, however, that uptake patterns are likely to be more sensitive to the prescribing behaviour of individual rheumatologists in the State/Territory where there are few rheumatologists (e.g. Tasmania) compared to those States/Territories with large numbers of rheumatologists (e.g. New South Wales). Findings from the interview study, reported in Chapter 3, offer some explanations for the variation in the prescribing rates of the biologicals: (i) some rheumatologists were more cautious and conservative than others due to concerns about the longer-term, uncertain safety of the biologicals; at the time of interviews, the number of patients each rheumatologist treated with biologicals under the PBS ranged from 2 to 16; (ii) some rheumatologists appeared to be more conscious of the societal costs of their prescribing than others; and (iii) the level of assistance (e.g. from nurses) available for the substantial amount of paperwork required to gain access for their patients. There was no apparent association between the demographic characteristics (age, gender, and years of clinical practice) of the eight rheumatologists who participated in the qualitative study and the number of patients each treated with biologicals under the PBS (Chapter 3). Literature suggests several reasons for variations in prescribing patterns in general. These include: the influence of opinion leaders, local traditions and local clinical guidelines, some physicians are early adopters of new therapies, and the influence of marketing by pharmaceutical companies is a major driving forces behind the prescribing of newer drugs.(429, 430) The wide variation in

prescribing rates associated with the anti-rheumatic biologicals is an important finding of the current study and warrants further research to systematically investigate the possible reasons for this variability.

Literature also indicates that the goal of equitable access to medicines is yet to be achieved in other countries. Geographical variation in access to biologicals and other prescription medicines has been identified in the United Kingdom (termed 'post code prescribing' to describe variations in the availability of different treatments across different areas). This is partly because National Institute for Health and Clinical Excellence (NICE) is only responsible for providing evidence-based guidance but is not responsible for the funding of new medicines/technologies, and it does not consider affordability issues of regional funding bodies with limited budgets. Local authorities, hospital trusts and primary care groups/trusts under the National Health Service, although required to apply prescribing guidance produced by NICE, do not always recommend prescribing of some drugs until more data is available (i.e. delayed, 'patchy' implementation).(431, 432) In addition, there is some form of limitation in prescribing of biologicals implemented by different funding bodies, such as capped funding or fixed number of patients to be treated per month; long waiting times for patients to receive the biologicals after gaining approval for access has also been reported.(433) In the USA, significant differences in the use of biologicals between RA patients in health maintenance organisations and other forms of managed care (including both preferred provider organisations and point-of-service plans) and fee-for-service settings have also been identified.(434) Inconsistencies in reimbursement strategies across the various funding schemes potentially impede access to these agents.(435) Access to etanercept is restricted by "prior authorisation" in the majority of managed care organisations (68%).(436) Further, higher usage of infliximab than etanercept reflecting preferential Medicare

reimbursement for drugs administered by infusion under the former Medicare policy has been reported, indicating that unequal reimbursement for different treatments has an impact on physicians' choice of therapies.(437)

The heterogeneity in publicly-funded access to prescription medicines in other medical areas has also been identified. Variations in the use of cancer drugs cross England was reported using aggregated data on drugs prescribed and administered.(438) A study conducted before the newly introduced Medicare Prescription Drug, Improvement, and Modernisation Act of 2003 in the USA reported that Medicare reimbursement criteria influenced the prescribing of (and thus patients' access to) more costly chemotherapies for the treatment of metastatic breast, colorectal, and lung cancers.(439) Studies have demonstrated that prescription drug coverage varies across provinces in Canada,(440, 441) including access to anti-cancer drugs.(442) A centralised review mechanism, Common Drug Review, was launched in 2004 (all provinces are participating with the exception of Quebec). This centralised drug review, although has an advisory role only at this stage, may lead to more consistent formulary decision-making across provinces and equalise access to prescriptions drugs across Canada.(443)

As found by this study, the government expenditure on anti-rheumatic biologicals increased steadily over the first two years of PBS-subsidy (Figure 5.6). Essentially the vast majority of the cost of biologicals is covered by the government (99.5%) with a minimal proportion contributed by patients through co-payments. The majority of expenditure on biologicals was in support of concessional patients. This is not surprising as the PBS restrictions select for those patients with severe RA who are likely to suffer from functional disability. Loss of work capacity in RA patients has

been well recognised.(444) Monthly PBS expenditure on anti-rheumatic drugs overall (including both DMARDs and the biologicals) has more than doubled since the biologicals became available (Figure 5.6). This increasing expenditure on medicines for RA and the relatively high cost of biologicals need to be examined together with other expenditure such as cost of monitoring and treating adverse reactions as well as the cost of managing RA: direct costs such as other health services, indirect costs such as work disability, and intangible costs such as pain, fatigue, and psychological distress.(445) The potential that these treatments may obviate the need for surgical procedures such as joint replacement or synovectomy associated with joint destruction and progressive functional disability characteristic of inappropriately controlled RA (i.e. cost savings) needs also to be taken into consideration.(446)

Rheumatoid arthritis is associated with considerable socio-economic impact on individual patients and their families as well as on society as a whole.(227, 445, 447-449) Effective and timely pharmacological management of RA potentially reduces individual and societal costs. An estimated A$246 million spent on health services including 19% on pharmaceuticals (prescribed and over-the-counter medications) in the year 2000/01 was attributable to RA in Australia.(408) These data are concordant with a previous report that 8-24% of the direct cost of treating RA could be attributed to the cost of drugs.(450) The use of biologicals may influence the use of other services. For example, a small study in the United Kingdom reported a 55% reduction of in-patient services use while the use of out-patient services doubled,(451) an important factor which also needs to be examined. Further, additional resources are needed to administer the PBS criteria and this process is expensive because of its complexity (Chapter 3). Formal review of these expenses

is warranted to understand the value of such controlled access schemes for medicines and as a basis from which to enhance value.

While aggregated claims data can provide useful insights into uptake of biologicals and of prescribing trends, there are several limitations associated with this method of analysing drug usage and expenditure data. The population-level data discussed here were derived from the Medicare Australia national administrative database, which is readily available through its web-site. The number of patients using a biological agent under the PBS can only be approximated from these figures. It was not possible to determine the proportion of patients that were approved to continue or switch between biologicals, as noted. The characteristics (e.g. age and sex) and clinical details (e.g. joint counts and concomitant medicines) of patients using the biological therapies cannot be examined. The questions as to whether the current level of utilisation represents appropriate or inappropriate prescribing of biologicals in Australia, and whether this usage sufficiently or insufficiently meets the needs of RA patients cannot be addressed on the basis of this analysis of aggregated data and lack of sound epidemiological data on RA in Australia. The impact of the 'continuation rule' on access to high-cost medicines such as the biologicals is not clear and an area that still needs to be addressed. De-identified, individual data on patient demographics and use of subsidised prescription medicines that can be purchased from Medicare Australia may provide some of this information. However, accessing this data is difficult, and there is a lack of outcomes data available on high cost biologicals for evaluation despite the fact that clinical information on each patient has been collected (described in Section 4.3). Further, linkage of data sets cross jurisdictions is currently not feasible on a national level (described in Section 4.2). This study emphasised the value that would accrue from availability of more comprehensive, de-identified, individual patient data that would enable more

detailed examination of utilisation of medicines. Australia lags behind other countries in the area of readily available, individual-level comprehensive datasets that can potentially identify and address important issues, including utilisation of medicines, and access to and quality of healthcare (described in Section 4.5).

In conclusion, utilisation of high-cost, anti-rheumatic biologicals in Australia over the first two years of PBS subsidy has been conservative, well below forecast but with considerable variability across States and Territories, usage roughly correlating with access to rheumatologists. Recent increased transparency of projections of utilisation and expenditure on medicines is useful for future evaluation of utilisation of medicines against projections. Evaluation based on individual-level comprehensive data (i.e. medicine use, and health and economic outcomes data) would enable a more detailed examination of the usage patterns of medicines and associated outcomes in Australia. Such feedback is essential for decision makers to refine the criteria and for prescribers to manage patients appropriately and cost-effectively. It is time to make the data available for approved, ethical research in the interests of better outcomes from medicines supplied under the national subsidy program, the Pharmaceutical Benefits Scheme.

6. THE IMPACT OF CONTROLLED ACCESS TO BIOLOGICAL MEDICINES ON THE UTILISATION OF CONVENTIONAL DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS

A pre-requisite to access the biological agents for the treatment of rheumatoid arthritis under Australia's Pharmaceutical Benefits Scheme (PBS) is evidence of an adequate trial of conventional disease-modifying anti-rheumatic drugs (DMARDs). This chapter reports a study examining whether there are changes in prescribing of DMARDs since the introduction of the PBS-criteria for access to biologicals, in August 2003.

6.1 Introduction

Traditional disease-modifying anti-rheumatic drugs (DMARDs) are used as mono- or combination therapies and are the mainstay of rheumatoid arthritis (RA) treatment. Non-steroidal anti-inflammatory drugs and/or corticosteroids may be used in combination with anti-rheumatic drugs. The early and aggressive use of DMARDs has been well-demonstrated to enhance the control of disease activity, reduce joint erosions and improve quality of life in patients with RA.(228, 452-457) However, the recent introduction of biological response modifiers has changed the management of RA dramatically. Biological agents reduce the signs and symptoms of RA, improve physical function, and inhibit the progression of structural joint damage more effectively than conventional DMARDs,(232, 426, 458-460) and have been shown to be relatively safe and effective in early RA.(458, 459, 461-463) Early intervention to slow the progression of joint destruction is important as greater joint

damage at baseline and in the early weeks of disease activity was associated with less improvement in physical function after treatment.(464)

Access to PBS-funded biologicals requires that patients have an adequate trial of conventional DMARDs. This 'treatment algorithm' includes methotrexate (specified minimum dosage of 20 mg/week), a combination of three DMARDs (including methotrexate of at least 7.5 mg/week) for at least three months, and leflunomide (with or without methotrexate) or cyclosporin for a further three months (described in Chapter 2, Figure 2.4). Among the DMARDs available in Australia, leflunomide is the only 'authority required' medicine specifically restricted to the treatment of RA under the PBS (subsidised since February 2000), and is also one DMARD specified by the PBS that patients must trial before they can be considered eligible for biologicals.

The majority of prescription medicines used in Australia (~90% of prescriptions dispensed) are subsidised by the PBS. Studies have found that PBS restrictions have important influences on prescribing patterns and medicine use.(303, 332) The PBS-mandated 'treatment algorithm' for access to biologicals is generally in accord with the contemporary approach of more aggressive use of DMARDs,(465) and, thus, might be considered to be promoting evidence-based treatment. Therefore, the use of DMARDs could provide a measure of the influence of PBS restrictions on prescribing patterns of rheumatologists and act as a surrogate indicator of adherence to recommendations for aggressive therapy with DMARDs in RA patients. Further, all new and novel arrangements for access to medicines made available via the PBS and similar entities ought to be subject to rigorous evaluation of their effects in order to optimise health, economic and societal outcomes.

6.2 Study aim

The aims of this study were to examine national trends in the utilisation of DMARDs over the period 2000-2005 and to determine whether the utilisation trends have changed as a result of introducing the PBS access criteria for biologicals in August 2003.

6.3 Methods

6.3.1 Data collection

Monthly prescription and expenditure data for the five-year period, August 2000 to June 2005, were obtained from the Drug Utilisation Sub-Committee (DUSC) of the PBAC (via a written request – Appendix 6.1). Patient age and gender summary files for these prescription data were also requested.

DUSC maintains a database of prescription medicines dispensed to the Australian community (described in Section 4.4).(288) Although only estimates on dispensing of non-subsidised prescription medicines from a sample of pharmacies are included in the DUSC data, the combined DUSC data is useful for examining the use of DMARDs in the community because most of these drugs are priced below the general co-payment threshold.

This study was exempted from full ethics review by the Executive of the Human Research Ethics Committee of University of New South Wales, Australia.

6.3.2 Data analysis

National trends in the use of DMARDs were examined using aggregated monthly prescription data. Utilisation data for July 2005 was not available at the time of the study; utilisation for the year Aug 2004-Jul 2005 was annualised based on the Aug 2004-Jun 2005 data.

DUSC provided monthly data for six medicines used mainly as DMARDs for treating RA: methotrexate, hydroxychloroquine, penicillamine, sulfasalazine, gold preparations (sodium aurothiomalate and auranofin), and leflunomide. These medicines were available in a total of 15 formulations under the PBS (Table 6.1).

Table 6.1 DMARDs included in the present study

PBS item number	Drug	Form and quantity
1095P	Auranofin	tablet 3 mg 60
2016D	Sodium aurothiomalate	injection 10 mg 10
2017E	Sodium aurothiomalate	injection 20 mg 10
2018F	Sodium aurothiomalate	injection 50 mg 10
2721F	Penicillamine	tablet 125 mg 100
2838J	Penicillamine	tablet 250 mg 100
1512N	Hydroxychloroquine	tablet 200 mg 100
1622J	Methotrexate	tablet 2.5 mg 30
1623K	Methotrexate	tablet 10 mg 50
2396D	Methotrexate	injection 5 mg/2mL 5
2093E	Sulfasalazine	tablet 500 mg 200
2096H	Sulfasalazine enteric-coated	tablet 500 mg 200
8373Q	Leflunomide	tablet 100 mg 3 & 20 mg 30
8374R	Leflunomide	tablet 10 mg 30
8375T	Leflunomide	tablet 20 mg 30

The specific indication for which DMARDs were prescribed is not captured by the DUSC data. Although some DMARDs are used in indications other than RA, major changes in prescribing rates in RA should be reflected in the DUSC data because of the relatively higher prevalence of RA (1%). For example, sulfasalazine is also used in the treatment of inflammatory bowel disease (approximately 10,000 people are affected by inflammatory bowel disease in Australia, that is, 0.05% prevalence (466) which is substantially lower than RA). Also, not all patients with inflammatory bowel disease are prescribed sulfasalazine. Methotrexate is used for treating cancer, but the low-dose injection and oral forms included in this study are not used for this indication. Methotrexate is also used for the treatment of other rheumatic conditions such as psoriatic arthritis and ankylosing spondylitis; the prevalence of these conditions is considerably less (both are about 0.1%) than RA and methotrexate is not used in all of these patients. The data for methotrexate are thus further unclear because of this confounder. By contrast, leflunomide is specifically restricted to the treatment of RA under the PBS ('authority required') as noted, thus dispensing data on leflunomide do reflect use in the treatment of RA only. Prescriptions of leflunomide and methotrexate over the study period were examined separately.

It should be acknowledged that a proportion of DMARD usage in the Northern Territory and in remote areas is distributed through the Aboriginal and Torres Strait Islander Health Services under Section 100 of the *National Health Act 1953* and these data are not captured by Medicare Australia or DUSC.(414)

6.4 Results

6.4.1 Utilisation of DMARDs over the period 2000-2005

This section has been published ("*Has the use of disease-modifying anti-rheumatic drugs changed as a consequence of controlled access to high-cost biological agents through the Pharmaceutical Benefits Scheme?*" Intern Med J 2007, in press).

Monthly data on national trends in use of aggregated DMARDs revealed a steady increase in the period August 2000 to June 2005 without an inflexion around the time PBS-criteria for the biologicals were introduced (Figure 6.1). There were 2,887,746 prescriptions for all DMARDs dispensed during the study period and 95% of these were prescriptions under the PBS and Repatriation Pharmaceutical Benefits Scheme (RPBS). Government expenditure for these was A$156 million. Averaged monthly expenditure on DMARDs increased from A$2.3 million in 2000 to A$2.85 million in 2005 (22.6% increase). Patient age and gender summary files were not available to us from DUSC at the time of the study. Over the five-year period, the Australian population increased by approximately 6%,(467) which would account for some of the increase in DMARD prescriptions.
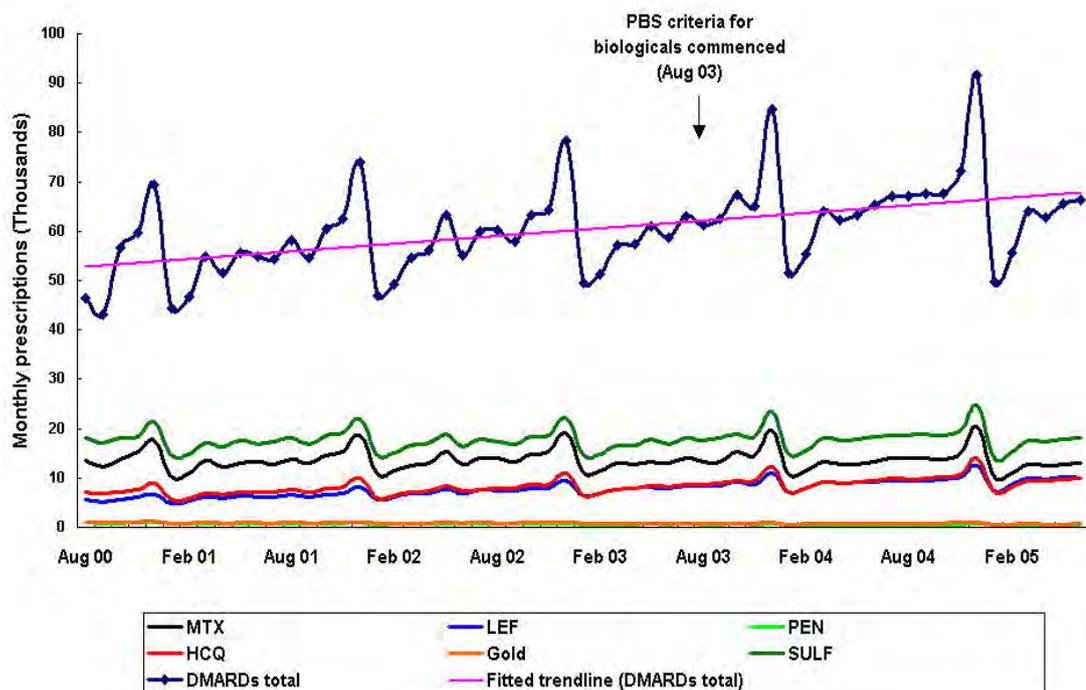
Figure 6.1 Monthly prescriptions of DMARDs based on DUSC data (Aug 2000-Jun 2005)

Gold=sodium aurothiomalate and auranofin, HCQ=hydroxychloroquine, LEF=leflunomide, MTX=methotrexate, PEN=penicillamine, SULF=sulfasalazine

Peaks at the end of each year (Figure 6.1) represent the well-recognised effect of the 'safety net' driven stockpiling of medications, i.e. more prescriptions are dispensed towards the end of each calendar year and a lower prescription volume is observed at the beginning of the subsequent year.(337)

Between August 2000 and July 2005, aggregate annual prescriptions of DMARDs increased by 16.7% from 541,718 in year 1 to an annualised 631,996 prescriptions in year 5; increasing by approximately 4% per year (Figure 6.1, Table 6.2). Based on prescription volume, sulfasalazine was the most prescribed DMARD, accounting for 37% of all prescriptions; its use was steady during the study period (a proportion of sulfasalazine prescriptions is expected for inflammatory bowel disease, however). The use of gold preparations and penicillamine was low with a downward trend, of

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approximately 7% and 10% per year, respectively. There was a steady upward trend in the use of hydroxychloroquine, of approximately 9% per year over the study period (Figure 6.1).

Table 6.2 Prescriptions of DMARDs based on DUSC dispensing data (Aug 2000-Jul 2005)

	Aug 00-Jul 01	Aug 01-Jul 02	Aug 02-Jul 03	Aug 03-Jul 04	Aug 04-Jul 05*	Total**
MTX total	158,293	164,768	164,954	164,154	163,190	801,760
MTX 2.5 mg	122,684	120,892	115,387	105,919	96,580	553,414
MTX 10 mg	34,216	42,390	48,361	56,926	65,447	241,886
MTX 5 mg/2mL	1,393	1,486	1,206	1,309	1,163	6,460
LEF total	70,223	82,162	93,563	106,558	116,623	459,410
LEF starter	2,550	999	671	491	279	4,967
LEF 10 mg	9,465	14,032	17,372	20,917	24,209	83,978
LEF 20 mg	58,208	67,131	75,520	85,150	92,134	370,465
PEN	9,952	9,385	7,945	7,007	6,442	40,194
HCQ	84,229	90,985	97,906	110,449	118,528	492,220
Gold	11,560	10,764	10,176	9,521	8,553	49,861
SULF	207,461	210,670	208,688	217,043	218,661	1,044,301
DMARD prescriptions	541,718	568,734	583,232	614,732	631,996	2,887,746
DMARD Government expenditure (A$)	27,905,612	29,976,399	32,310,372	34,376,571	34,213,392	155,931,230

MTX=methotrexate, LEF=leflunomide, PEN=penicillamine, HCQ=hydroxychloroquine, Gold=sodium aurothiomalate and auranofin, SULF=sulfasalazine
* Dispensing data for July 2005 was not supplied by DUSC, utilisation annualised based on Aug 2004-June 2005 data
** Total number of prescriptions and government expenditure from August 2000 to June 2005

PBS prescriptions accounted for practically all leflunomide dispensed in Australia (99.7%), there were 464,382 prescriptions and government expenditure for these was A$87 million. The use of leflunomide increased steadily by 13.5% per year over the study period. The use of starter packs of leflunomide declined substantially however (by 89% between 2000 and 2005), as a consequence of high rates of diarrhoea experienced with their use due to high loading dose. There was an upward trend in the use of leflunomide 10 mg tablets and 20 mg tablets, steadily increasing by approximately 27% and 12% per year, respectively (Figure 6.2).
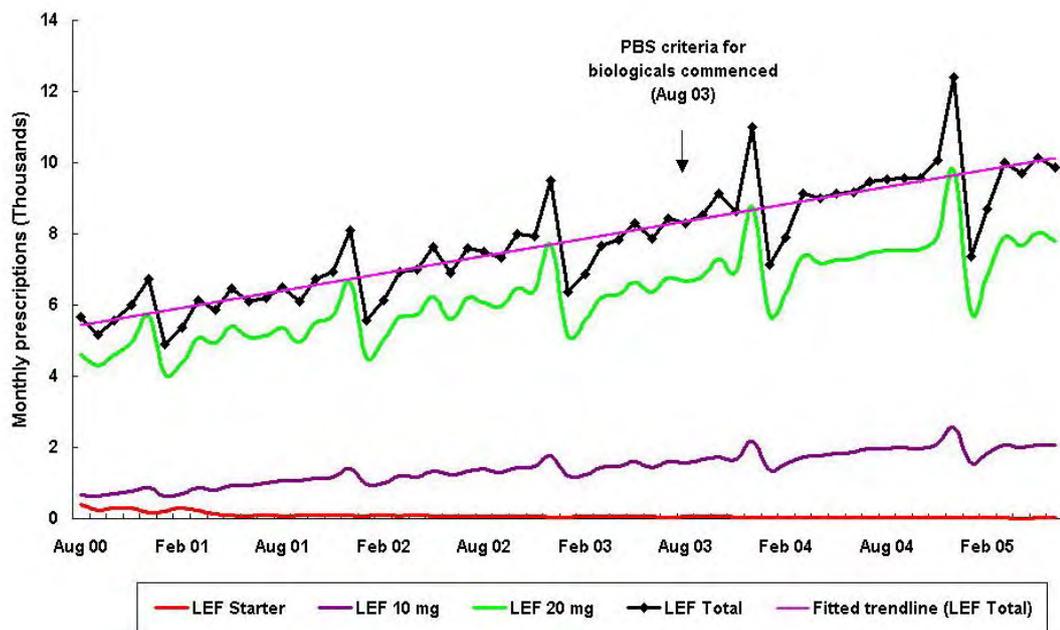
Figure 6.2 Monthly prescriptions of leflunomide based on DUSC data (Aug 2000-Jun 2005)

LEF=leflunomide

There was a small downward trend in methotrexate use over the study period. Use of methotrexate 5 mg/2mL injections was low and decreased by approximately 3.7% per year. The use of methotrexate 2.5 mg tablets decreased by 5.7% per year, while the use of 10 mg tablets steadily increased by approximately 17.7% per year over these five years (Figure 6.3).
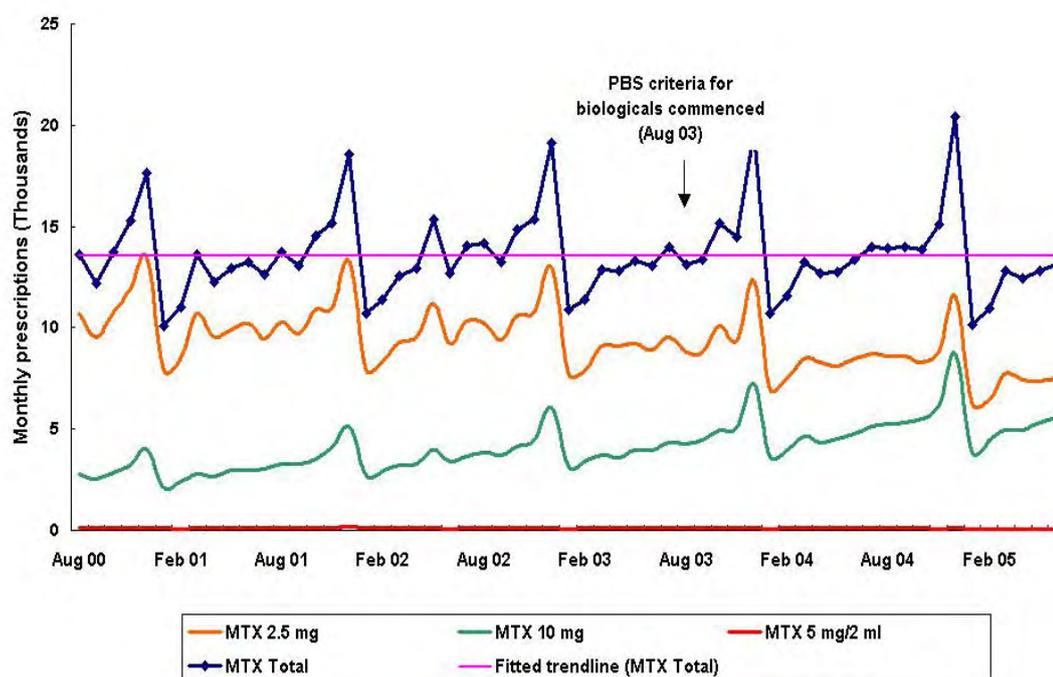
Figure 6.3 Monthly prescriptions of methotrexate based on DUSC data (Aug 2000-Jun 2005)

MTX=methotrexate

6.4.2 Utilisation of leflunomide by Australian States and Territories

As noted in Section 6.3.2, dispensing data for leflunomide reflect specifically use in the treatment of RA. Over the five-year period, utilisation of leflunomide was highest in New South Wales (6,716,277 prescriptions), as illustrated in Table 6.3. The relative *per capita* uptake of leflunomide indicates that Tasmania, Western Australia, and the Australian Capital Territory had the highest uptakes (370.8, 292.2, and

264.0 prescriptions per 10,000 population, respectively). The Northern Territory had the lowest *per capita* use – 88.9 prescriptions per 10,000 population (Table 6.3). There was thus a 4-fold difference in *per capita* use between the jurisdictions.

However, prescribing rates of DMARDs by rheumatologists across the States/Territories cannot be calculated. This is due to several reasons: (i) adjusting the number of leflunomide prescriptions for State rheumatologist numbers is not appropriate because prescribing of DMARDs (including leflunomide) is not restricted to rheumatologists under the PBS, (ii) while DMARD prescription can be stratified according to the major specialty of the prescribing doctor, 'major specialty' of a doctor reported by Medicare Australia and by DUSC is categorised on the basis of his/her medical service claims rather than his/her medical specialty recognised by the Australian Medical Council, and (iii) DMARD prescription data according to the major specialty of the prescribers provided by DUSC were not stratified by States/Territories.

Table 6.3 Prescriptions of leflunomide for RA by Australian States and Territories based on DUSC dispensing data (Aug 2000-Jun 2005)

	NSW	VIC	QLD	SA	WA	TAS	ACT	NT
LEF total	139331	114415	70063	35776	57541	17795	8516	1767
LEF prescriptions per 10,000 population[a]	207.5	231.2	182.5	233.6	292.2	370.8	264.0	88.9

[a] Source: Australian Bureau of Statistics, Australian Population – States and Territories, December quarter, 2003.
LEF= leflunomide
Australian States/Territories: NSW = New South Wales, VIC = Victoria, QLD = Queensland, SA = South Australia, WA = Western Australia, TAS = Tasmania, ACT = Australian Capital Territory, NT = Northern Territory

6.4.3 Utilisation of leflunomide by rural, remote and metropolitan areas

Based on the population-adjusted DUSC dispensing data for leflunomide, prescribers in the capital cities provided 22% of prescriptions. Prescribers in other metropolitan centres and in small rural centres provided 18% of prescriptions, and prescribers in the large rural centres provided a further 16% of prescriptions (Table 6.4).

Table 6.4 Prescriptions of leflunomide by Rural, Remote, and Metropolitan Areas (RRMA) classification system based on DUSC data (Aug 2000-Jun 2005)

	Prescriptions per 10,000 population[a]	
RRMA	Leflunomide Total	% of Total
Capital cities	260.6	21.7
Other metropolitan centres	223.1	18.6
Large rural centres	189.1	15.8
Small rural centres	217.5	18.1
Other rural areas	135.2	11.3
Remote areas	98.3	8.2
Other remote areas	76.2	6.4

[a] Source: Population estimates from Australian Institute of Health and Welfare, based on 2001 census data.(339)

6.5 Discussion

Prescriptions of DMARDs in aggregate increased steadily from 2000 to 2005. The trends in the utilisation of individual DMARD agent as well as overall DMARDs continued without a discernable change over the two years following the introduction of the PBS-criteria for access to biologicals for RA. Over the five-year period, uptake of leflunomide, the only conventional DMARD specifically used in the treatment of RA under the PBS, demonstrated some variability across States and Territories. A small variability was also observed across the rural, remote and metropolitan areas.

Arthritis is one of Australia's National Health Priority Areas.(468) Effective and timely pharmacological management of RA potentially reduces individual and societal costs. Subsidisation of biologicals for Australian patients was much anticipated but had been delayed compared to other countries, only being introduced into Australia under the PBS in 2003; the time from marketing approval of etanercept to PBS-listing was 40 months.(216) It was expected that rheumatologists and patients might subscribe heavily to the 'treatment algorithm' that was required to access the biologicals because of the widely anticipated efficacy of these new agents. A sudden upsurge in the national prescription trends of DMARDs around the time of the introduction of PBS-criteria for biologicals could indicate that Australian rheumatologists had not been treating RA as aggressively as guidelines and evidence recommended. The findings of this study indicate that DMARD usage trends that were increasing pre 2003 did not alter post the introduction of biologicals. However, whether the availability of PBS-subsidised biologicals and the accompanying 'treatment algorithm' had had an effect on prescribing behaviour of rheumatologists cannot be definitively concluded from this study based on aggregated data.

Seasonal variations seen in the uptake of DMARD prescriptions (Figures 6.1, 6.2 and 6.3) reflect the strong effect of the 'safety net scheme' on the pattern of PBS drug utilisation. The 'safety net scheme' for the PBS, which operates over a calendar year, is designed to protect those patients and their families who require a large number of prescription medicines on the PBS and RPBS. Once patients reach a certain spending level ('safety net threshold'), they are qualified to receive R/PBS medicines at a reduced co-payment or free of charge for the rest of that year.(469) It is recognised that the safety net scheme is associated with considerably higher prescription volumes in the final quarter of the calendar year, particularly during

December, and lower prescription volumes in the early stages of the next safety net year.(185, 470) While this seasonal variation was evident in DMARD prescription uptake, it was not observed in the uptake of biologicals (Chapter 5, Figure 5.5). The absence of seasonal variation is likely to be associated with the fact that the biological medicines are 'authority required' prescription items with a 'continuation rule', i.e. patients are required to demonstrate adequate clinical improvement before approved for continuing therapy. As a consequence, the behaviour of filling prescriptions before the original or previous supply of medicine has been consumed is possibly constrained by these PBS restrictions.

The increase in DMARD prescriptions (16.7%) was greater than the increase in the Australian population (6%) over these five years. Also, the reported incidence of RA in Australia is approximately 0.4 cases per 1,000 persons i.e. 0.04% per annum (global incidence ranges from 0.2 to 3 cases per 1,000 persons, depending on race and year of study).(408) Thus, the stable increase in DMARD prescriptions revealed in this study (16.7%) exceeds that expected from the population increase and the incidence of RA, notwithstanding the effects of patients stopping DMARD therapy due to death or other causes. This suggests that patients with RA in Australia are increasingly likely to have been managed according to contemporary guidelines that advise prescribing DMARDs earlier and more aggressively in the course of RA. In addition, the stable upward trend in the use of leflunomide (both 10 mg and 20 mg tablets) and methotrexate 10 mg also suggest that patients with RA in Australia are generally being managed more aggressively. However, it should be acknowledged that alternative explanations for the increased use of methotrexate 10 mg (and decline in the use of methotrexate 2.5 mg) are that: (i) it is more economical for patients to use 10 mg tablets and split tablets if required (e.g. 15 mg given as one and a half tablets) and (ii) combination use is being avoided in order to prevent

administration errors that may occur because 2.5 mg and 10 mg tablets are similar in appearance. Nonetheless, the very low use of penicillamine also suggests evidence-based practice because penicillamine is ineffective in suppressing bone erosions.(471) The findings of this study concur with those of Chan and Tett (472) who also found increasing use of DMARDs in Australia from 1992 to 2004, using data from Medicare Australia (estimates of non-subsidised use were not included). These investigators suggested that their finding reflected earlier and more aggressive use as well as more prescribing of DMARDs in combination to treat individuals with RA, conclusions concur with the findings of the present study.

As DMARDs have been available in the market for a relatively long time and their costs are relatively low, other influences such as promotional activity and the effects of variations in drug price on prescribing practices are expected to be minimal. Increasing patient co-payments potentially affects prescription uptake under the PBS, however, annual increases over the last decade have been small. There was a considerable increase of 25% in patient co-payment since 1 January 2005, but no significant downward trend in DMARD prescriptions was observed in relation to this increase.

The uptake of DMARDs over the next few years may not decrease significantly. Recent evidence suggests that the use of DMARDs in combination is as efficacious as a biological plus DMARD therapy.(473) Accumulating evidence also demonstrates that DMARDs are safe and efficacious when used in combination with biological agents, and such combination therapy appears to be more effective than treatment with a biological alone. A trial comparing etanercept alone with the combination of etanercept plus methotrexate demonstrated that addition of

methotrexate significantly increased the efficacy of etanercept.(427) Results of small studies suggest that the combination of infliximab with leflunomide may be effective with no increase in toxicity;(474, 475) however, these studies are limited by their small size and lack of comparison group. Recent findings from population-based observational studies demonstrated that DMARDs (other than methotrexate) such as sulfasalazine, hydroxychloroquine, gold, and leflunomide are safe and efficacious in combination with etanercept,(388, 476) and there is some other evidence supporting the combination of these DMARDs with infliximab.(381, 388) Further, combination therapy appears to be more effective in preventing joint damage than treatment with biological alone.(477) Longer-term data is warranted to confirm the safety and efficacy of the combination therapy of biologicals with DMARDs (other than methotrexate).

Interpretation of changes in the trends in use of DMARDs is quite limited because the dispensing data provided by DUSC is aggregated and not linked to an individual patient. Thus, changes in the choice and mix of drugs and their dosage are inaccessible using this data source. For example, any increase in use of DMARDs as influenced by the 'treatment algorithm' could be offset by declines in use of DMARDs due to improved clinical outcomes in patients who are treated with biologicals, or simply because of switching to biologicals from DMARDs.

As noted previously, leflunomide, unlike other DMARDs included in this analysis, is specifically used in the treatment of RA under the PBS, thus its utilisation pattern may be compared with that for anti-rheumatic biologicals. Population-adjusted utilisation of leflunomide by States and Territories indicates some geographical variation (Section 6.4.2); there was a 4-fold difference between the jurisdictions for

the highest and lowest relative *per capita* uptakes (Table 6.3). This variation was half of that observed for the utilisation of biologicals (an 8-fold difference between the jurisdictions; Chapter 5), although the trends were similar. Population-adjusted utilisation of leflunomide by rural, remote and metropolitan areas also indicates some regional variation (Section 6.4.3); for which there was a 3-fold difference in relative *per capita* uptake between the jurisdictions (Table 6.4). This variation was significantly less than that observed for the utilisation of biologicals across the rural, remote and metropolitan areas (an 83-fold variability; Chapter 5). By contrast to the biologicals, prescribing of leflunomide is not restricted to rheumatologists. Therefore, accessibility to general practitioners who are allowed to prescribe leflunomide under the PBS is possibly associated with the significantly smaller variation in uptake. This is because *per capita* access to general practitioners is substantially higher than that for rheumatologists (14 general practitioners per 10,000 population (478) versus 0.126 rheumatologist per 10,000 population). The rate of prescribing by general practitioners by States/Territories, however, cannot be estimated from the PBS data that is available for external analysis.

While the variability observed in the uptake of biologicals was roughly correlated with accessibility to rheumatologists as noted, more definitive conclusions about the impact of individual rheumatology practice on the variation across the country cannot be reached by this study. The average prescribing rate of DMARDs (including leflunomide) by rheumatologists across the States/Territories cannot be calculated from the accessible, aggregated prescription data (Section 6.4.2). Therefore, the prescribing patterns of DMARDs and biologicals of individual rheumatologists could not be compared. Findings of the interview study (Chapter 3), however, suggest that differences in prescribing patterns of individual

rheumatologists with respect to anti-rheumatic drugs are likely to contribute, at least to some degree, to the geographical variation in biological utilisation.

These serious limitations to interpreting drug usage trends would be easily rectified by allowing easier access to de-identified, individual, longitudinal data on prescription claims and medical services claims. These data are already collected by Medicare Australia and the Commonwealth Department of Health and Ageing. Important hypotheses relevant to public health could then be examined with the general goal of service improvement. De-identified, individual data on patient demographics and utilisation of medicines can be purchased from Medicare Australia for ethically and scientifically sound studies. However, accessing these data is slow and difficult, and individual-level data on health outcomes are not readily available (Chapter 4). Further, data on the use of medical services such as joint replacement are not routinely linked to drug utilisation for de-identified individuals.(309) Data on the utilisation of medicines in hospitals and actual usage rather than estimates of non-subsidised prescription medicines are also not available. The indication for which medicines are prescribed is not captured by either the Medicare Australia database or the DUSC database. Lack of clinical indications for prescribed medicines and dosing information is also a limitation of other administrative databases.(296)

Analyses based on individual-level comprehensive data are warranted to examine the impact of the introduction of PBS-criteria governing access to biologicals. These drugs are used to treat a serious chronic medical condition that is designated a national health priority and there are many important questions that should be answered. For example, pertinent questions include: what have been the changes in

the number of patients taking DMARDs since the subsidy of biologicals; what changes have occurred in the selection of DMARDs or their dosage and the resultant health outcomes? what are the health outcomes of patients taking DMARDs and biologicals concomitantly? and what are the associated economic outcomes of different treatment strategies? A review of historical patient and utilisation data should and could be conducted to assess whether trends are apparent. Historical evidence is required in order to properly understand the effects of interventions such as the introduction of new pharmaceutical options under the PBS or PBS restriction changes. Time-series analysis of individual-level claims data is the most suitable technique for providing meaningful insights into the effects of changes in access to important medicines and examples abound of the value of this approach.(158, 303, 479, 480) Alternatively, observational studies using data collected by patient registries such as the Australian Rheumatology Association Database would also provide useful information.

Observational databases are an important source of information on therapeutic behaviour and changes. For example, the General Practice Research Database in the United Kingdom (UK) contains the primary care records of 7 million individuals including information on clinical events, hospital referrals, hospital admissions and major outcomes. This database has provided a powerful resource to examine the history of DMARD prescribing for a large number of RA patients. It became apparent that a significant proportion of RA patients (about 50% of a total of 34,364 individuals identified with a clinical diagnosis of RA) was not appropriately treated in the UK when national data was examined between 1987 and 2002.(481) Further, studies using surveillance registries have identified considerable variation in drug and non-drug treatment indicating significant differences in healthcare provision and heterogeneity in the treatment strategies of individual rheumatologists,(482) and

areas of unwarranted variation in utilisation of DMARDs.(483) Whether PBS criteria for access to biologicals will lead to more uniform treatment strategies and improvement of outcomes remains to be determined but, again, the question could be more precisely addressed with timely access to de-identified, longitudinal, and individual patient data from available national data sets.

In summary, based on aggregated dispensing data, trends in national utilisation of conventional, non-biological anti-rheumatic drugs have not changed since the introduction of PBS-subsidised biologicals and the accompanying 'treatment algorithm'. Uptake of leflunomide demonstrated less variability across the States and Territories than that observed for biologicals, although the trends were similar. Prescribing restrictions imposed by the PBS potentially have important influences on clinical practice, such as standardising therapeutic approaches as a result of conforming to the PBS-criteria for access. Examination of prescribing patterns and feedback to stakeholders, but notably prescribers, is important to allow decision makers as well as prescribers not only to improve the PBS system but also to improve the management of individual patients. However, important changes in practice and outcomes may not be apparent without examining de-identified individual data over time. The ability to carry out such studies without impediment should now be a high national priority. In turn, evidence from rigorous, comprehensive evaluations will better inform policy development on access to medicines under the PBS with the goal to optimise the health and well-being of patients within fiscal restraints.

7. ACCESS TO HIGH-COST ANTI-RHEUMATIC BIOLOGICAL MEDICINES: ETHICAL PERSPECTIVES

"How should fair decisions about limits be made? Under what conditions should we view such decisions as a legitimate exercise of moral authority?" – Norman Daniels

The Pharmaceutical Benefits Scheme (PBS) is Australia's system for ensuring equitable access to prescription medicines for individuals and the society as a whole. It is important that any restrictions on access to medicines, in attempting to balance the benefits, risks, and costs, involve explicit consideration of ethical principles. Ethical principles should underpin our system of access to medicines in order to achieve the fairest outcomes for individual patients, as well as for the community. In this chapter, the access arrangements for high-cost medicines via the PBS are examined from an ethical perspective, using the biological agents for the treatment of rheumatoid arthritis as an example.

7.1   Introduction

Access to medicines is an integral component of Australia's National Medicines Policy. The significance of the National Medicines Policy is that it recognises the interdependence and tensions inherent within the four objectives of the policy, these being: attaining affordable access to medicines, industry development, quality use of medicines, and system for ensuring quality, safety and efficacy of medicines (as described in Chapter 2). Notably, a major tension is finding an appropriate balance between meeting the needs of an individual and those of the community. The Pharmaceutical Benefits Scheme (PBS) is Australia's system for ensuring equitable

access to prescription medicines. The PBS is inherently a communal or mutual scheme. Resources are pooled from society to benefit those who are ill. Although not formally established on the basis of an ethical framework, the underlying principle of the PBS is to provide universal access to safe, effective, necessary medicines at an affordable price, and it is a critical part of the process of achieving improved health outcomes.(85) It is clear that 'universal access' implies access to medicines by 'individual' patients.

For medicines subsidised by the PBS, use is targeted to the subgroups of patients who are likely to benefit most, that is, where cost-effectiveness has been demonstrated. Generally an 'authority' is required to access particularly expensive medicines. Clinical and laboratory-based measures are usually used to assess patient eligibility objectively. The administrative agency – Medicare Australia is an important partner to the PBS in this function of ensuring eligibility for access thereby enabling access to medicines for the Australian community.

Provision of high-cost medicines (HCMs) through the PBS is a significant achievement from both the perspectives of the individual patient and the community. Prescribers for individual patients can apply for access on their patient's behalf, thus assisting that patient to gain benefit; the community has also gained benefit through wise use of public resources because the PBS has carefully examined the evidence and recommended subsidy. Further, the diligence of the PBS and Medicare Australia to ensure access to medicines and cost-effective use of scarce resources, broadly, satisfies the ethical principles of beneficence (which recognises an obligation to benefit others in healthcare) and fairness.(38) However, complex requirements for access, as for 'authority prescriptions' (Chapter 2), demonstrate an

unprecedented and markedly increased 'external' influence over clinical practice. Such approaches to ensure cost-effective use and, in effect, control costs, are generally deemed necessary, but there are important ethical considerations arising. There has been little formal consideration of these ethical dimensions. The premise supporting the present analysis is that optimal outcomes for individuals and the community accruing from the PBS now and in future will depend upon the ethical framework that underpins this access system. The PBS processes of decision-making relating to access criteria and implementation of PBS restrictions for HCMs are focussed upon. This analysis, therefore, is novel and it is hoped, influential in the debate about the purpose and functioning of the PBS. It seems likely that these considerations will have universal value as there are many attempts internationally to provide medicines and health services via public agencies based on equity of access but with constraints on resources for those systems.

"Justice requires meeting healthcare needs fairly under resource constraints, and this, in turn, requires setting limits to care" – Daniels and Sabin.(484) In the context of limited healthcare resources, how much should decision makers favour what produces the best outcome based on evidence as opposed to giving people a fair chance to benefit? (484) A utilitarian viewpoint might favour maximising the aggregate benefit by directing resources to the group of patients with the greatest expected benefit.(484-486) An egalitarian approach might opt for random allocation – "fair opportunity" – where everyone who might in any way benefit are given the same chance to benefit.(484, 487, 488) Australia's healthcare system generally adopts an egalitarian approach. While the PBS system provides universal access for all citizens (i.e. egalitarian approach) to a wide range of prescription medicines for treating a range of medical conditions, medicines are only PBS-listed if they are of acceptable cost-effectiveness (i.e. utilitarian approach). New and/or

costly medicines (particularly HCMs) are often restricted via "authority required prescribing" to sub-sets of patients in whom such use was considered by the Pharmaceutical Benefits Advisory Committee (PBAC) to be acceptably cost-effective (i.e. utilitarian concept). From another view, access to HCMs is prioritised to individuals with more advanced disease who have not been adequately controlled using cheaper available therapies. This approach which has been referred to as 'the Priority View', demonstrates concern for the worse-off members of society and is part of the pursuit of fairness, justified by the argument that the worse off have more urgent needs.(489) The literature on the ethics of priority setting in relation to healthcare resources is extensive. In general, to reach an agreement on "what" decisions should be made in healthcare priority setting is challenging,(52) particularly because priority setting is value-laden and often takes place in complex contexts with multiple conflicting interests and perspectives.(52, 490) In this chapter, only the ethical framework of "accountability for reasonableness" is discussed because it describes "how" to reach priority setting decisions that would be socially and ethically acceptable. This was considered a sufficient framework for the purpose of the present analysis, undertaken from the perspective of an outsider to the decision-making processes.

Decision-making around drug subsidy and access criteria can also be considered a Quality Use of Medicines activity. The principles inherent in the "accountability for reasonableness" framework are concordant with Australia's National Medicines Policy and Quality Use of Medicines frameworks as well as the building blocks that underpin strategies to achieve Quality Use of Medicines (Chapter 2). The ethical framework "accountability for reasonableness" is built on the premise that decision-making processes need to be "fair" (procedural justice approach), particularly when setting "limits". It was developed in the United States within Health Maintenance

Organisations,(56) and has been demonstrated to be applicable in publicly funded healthcare systems.(67) According to Daniels et al., the method for reaching decisions involving priority settings in healthcare should be ethically sensitive. The process should be publicly acceptable allowing all stakeholders (including decision makers) to be confident in the decisions made.(484) Decisions are meant to be made in an open, transparent way, based on sound reasoning, and there should be public accountability for the decisions and the rationale behind them.(491) In order to make legitimate and fair decisions on priorities, there are four conditions defined by "accountability for reasonableness" that must be satisfied: relevance, publicity, appeals, and enforcement (Table 7.1).(56, 492)

Table 7.1 Four conditions of "accountability for reasonableness" ethical framework (56, 492)

Condition	Description
Relevance	Decisions must be founded on reasons (i.e. evidence, values, and principles) that "fair minded" participants can agree are relevant to meeting healthcare needs under resource constraints in the context
Publicity (Transparency)	Priority setting decisions and their rationale must be publicly accessible
Appeals (Revision)	Mechanisms must be included for revising decisions in light of further evidence or arguments that other stakeholders might contribute
Enforcement	There must be voluntary or public regulation to ensure that the first three conditions are met

In recent years, research conducted on priority setting in healthcare has used this framework to evaluate the decision-making process for legitimacy and fairness, including decisions about medicines in specific healthcare settings (described in Chapter 1).(67-69) It has not been applied to an ethical analysis of the PBS

processes, with a principal focus on decision-making in regards to accessing HCMs in the Australian context. An examination of access to biologicals for the treatment of rheumatoid arthritis (RA) in Australia using the "accountability for reasonableness" framework now follows. Areas where this examination suggests possible improvements in systems such as the PBS are highlighted.

7.2 Relevance (Rationale behind PBS decisions)

PBS decisions are based on evidence primarily acquired from randomised, double-blind, controlled clinical trials. Furthermore, decisions are, in part, value judgements, and thus are influenced by the complex context within which they are made. This section discusses the PBS decisions from the point view of the "relevance" condition of the "accountability for reasonableness" ethical framework. Relevance, as defined by "accountability for reasonableness", requires that decisions must be founded on reasons (i.e. evidence, values, and principles) that "fair minded" participants can agree are relevant to deciding how to meet the diverse needs of a particular population given necessary resource constraints (Table 7.1). Fair-minded people are those who seek in principle "to cooperate with others on terms they can justify to each other".(484)

7.2.1 Evidence

The premise underpinning evidence-based medicine is that clinical practice should reflect the best available evidence. The PBS aspires to this standard. The PBAC has explicit rules for sponsors on what specific evidence is needed in a submission for PBS-listing (Table 7.2); these are publicly accessible.(187)

Table 7.2 Clinical and cost effectiveness requirements of a major submission by the pharmaceutical company sponsor to the PBAC for PBS subsidy (187)

- Description of the proposed drug
- Choice and description of a main comparator
- Description of search strategies for relevant clinical and economic data from the published literature and unpublished data from the pharmaceutical company
- Evidence from head-to-head randomised trials or meta-analysis of randomised trials involving a common reference (data from non-randomised studies, such as observational studies, also considered)
- Detailed description of the comparative randomised trials, including measures taken to minimise bias during the conduct of the trials, characteristics of the trials, analytical methods, patient-relevant outcomes (e.g. quality-adjusted life-years, life-years saved, or mortality rates)
- Interpretation of comparative results, whether there is a significant clinical advantage (efficacy, safety, and effectiveness) of the proposed drug over the main comparator
- Preliminary economic evaluation (e.g. cost-minimisation, cost-effective, cost-utility, and cost-benefit analyses) based on the evidence from the comparative randomised trials and calculate an incremental ratio
- Modelled economic evaluation
- Detailed description of the modelled evaluation: input variables, structure of the evaluation, results, sensitivity analysis, and an incremental cost-effectiveness ratio (use of resources such as medical and other health-related services relevant to drug therapies to be included e.g. medical services, diagnostic services, community-based and hospital services)
- Estimation of extent of use of the proposed drug and other drugs, estimation of financial implication for the PBS and for government health budgets

PBS restrictions and, similarly, most clinical guidelines, are based at least in part on evidence from randomised controlled trials (RCTs). RCTs have long been considered the 'gold standard' for assessing the efficacy and safety of therapeutic agents. This evidence-based approach for making population-based reimbursement decisions enables, in principle, decision makers, clinicians and patients to make better informed decisions and thereby use resources more effectively and contributes to the effectiveness of decisions on resource allocation (taking into account benefits, harms, and level of evidence).(493-497) It is important to note, however, that the most appropriate clinical choice for an *individual patient* is not necessarily found in analyses of populations.(498, 499) Thus at times, PBS restrictions may not appear to be "relevant", a key principle of the "accountability for reasonableness" framework, to some individuals when access to medicines is

rationalised according to 'average' responses observed in RCTs. Generalisability is a recurring concern arising from RCTs because of restrictive eligibility requirements (e.g. minorities and the elderly are often excluded), small sample sizes, and short duration of therapy. In addition, patients who are participants in RCTs are a small, and often not a closely representative sample of real-world patients seen in everyday practice, for example in terms of disease activity, heterogeneity in clinical manifestations of a disease and co-morbidities.(340, 411, 500)

The goal of healthcare, stated in the Australia's National Medicines Policy,(238) is to achieve optimal health and economic outcomes for society as a whole and also for *individual* patients. Therefore, access criteria selected on the basis of evidence from RCTs potentially under-serve a minority of individuals. A relevant initiative by the National Medicines Policy committees in Australia recently has been to integrate "quality use of medicines" principles into the PBS-listing application review process in order to improve outcomes from medicine use,(264) as noted in previous chapters. This initiative foreshadows methods to more *precisely* deliver new medicines to the relevant subgroups of patients where acceptable cost-effectiveness has been demonstrated in the evidence submitted to PBAC (society as a whole) but in addition provide better access for the minority of individuals who currently 'miss-out' (individual patient).

7.2.2 Economic evaluations

Decisions about *public* benefit – resulting from control over access to highly specialised medicines – should be based on reasoned and balanced choices about benefits relative to both costs and risks of harm. This includes an economic evaluation. Economic evaluation is increasingly used to help prioritise provision of

treatments for different medical conditions in response to burgeoning demands for health care and the need to contain the costs. Economic evaluation, presented as being neutral and 'impartial', primarily focuses on efficiency and promoting *overall* welfare for the majority.(110) Whilst the majority of patients may benefit, not all individuals will. For the minority who are excluded by such economic analyses, the effect may be far from neutral. Economic analysis can override reasonable concerns held for the individual patient such that goals of treatment, rational selection of treatments, and the individual patient's experience and perspective are ignored.(501, 502) Thus leading to criticism of this approach.

Making reimbursement decisions is often challenging. Optimally, a formal assessment of economic factors, particularly costs and cost-offsets, is undertaken in pivotal RCTs but more commonly this is not the case so that other approaches are needed to examine cost-effectiveness. Economic evaluations are quite complex simulations that attempt to estimate the 'value for money' of the new drug compared to a comparator drug. However, the data inputs, usually from RCTs, and assumptions needed for such economic modelling, including choice and dose of comparator, are at the discretion of the sponsor.(503) Subjective judgements can contribute to considerable variation in the final findings,(504) and the previously mentioned 'neutral and impartial' claim for economic analysis is challenged. The Pharmaceutical Evaluation Section assesses economic evaluations submitted by the sponsors. Subsequently the Economic Sub-Committee of the PBAC assesses the evaluations conducted by the Pharmaceutical Evaluation Section and advises the PBAC. Undoubtedly these committees challenge assumptions, and may apply a more 'neutral' or conservative assumptions. It should be acknowledged that the data from early efficacy studies is inevitably limited and the quality of data with respect to its value in determining cost-effectiveness may be deficient. It is important that

economic evaluations make the best possible contribution to the decision-making process despite the deficiencies that may exist. The onus is on the decision makers to interpret the submitted data and analysis, and make a judgement they consider reasonable in a timely fashion. *However, this critical material is not available for external scrutiny*. Cost-effectiveness data comparing the new drug with available drug therapy is also pertinent to making the best clinical decision for a patient. The concept of making such material publicly accessible would have a degree of apparent legitimacy and is a requirement for stakeholder acceptance. This is because clinicians especially tend to favour a rights-based view of ethics in relationship to their individual patients, whereas the goal of economic evaluations is *utilitarian*. Thus, the 'relevance' of decisions cannot be discerned unless the basis for the decision is available for scrutiny by stakeholders outside the process (i.e. transparency; further discussed in Section 7.3).(505)

7.2.3 The context of PBS decisions

As defined by "accountability for reasonableness", a fair and legitimate decision should be based on rigorous evidence, and/or other reasons that are relevant and reasonable. Decisions about funding new drugs via a subsidy system such as the PBS are inherently based on not only scientific (clinical trial and economic) evidence, but also social values and expectations along with political considerations within the context that decisions are made.(506, 507) The decision-making context is characterised by its complexity.(508) The context of a population-policy level decision (namely the PBS decision-making context) is much more complex, uncertain and variable than an individual-clinical decision-making context.(507) Society's values (e.g. equity based on incremental cost-effectiveness) are the most relevant for reimbursement decisions, while the values of both patients and

clinicians might be more relevant for choosing treatment options in a clinical setting.(509) Understandably, the criteria for reimbursement are often more restrictive than the licensed indications for a new therapy. This is because the payers such as the PBS want to direct the use of the therapy towards those patients for whom it represents good value for money.(504, 509) Thus, besides clinical trial evidence of efficacy and effectiveness (which is not necessarily a good predictor of outcomes in clinical practice), decision makers at a policy level, namely the PBAC, reasonably considers a number of dimensions relating to cost-effectiveness, equity, feasibility and implementation in making its decisions on listing and access criteria (Table 7.3),(85, 216, 510) reflecting the Australian societal context in which its decisions are made.

Table 7.3 Dimensions considered by the PBAC in making a decision on drug subsidy (85, 216)

- Severity of the condition treated
- Presence of effective alternatives
- Ability to target therapy to those likely to benefit most
- Equity
- Comparative cost effectiveness
- Comparative health gain
- Affordability to the individual and the healthcare system (such as financial implication for the PBS)
- Uncertainties, such as those related to the clinical data or to the variability in sensitivity analysis of the economic model

George et al reviewed submissions made to the PBAC in the period 1991-1996 and reported that drugs for which the incremental cost per life-year[2] gained is less than A$42,000 (1998/99 values) tend to be recommended while drugs with a incremental cost per life-year gained over A$76,000 tend not to be recommended for PBS-

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[2] Life-year is "an outcome measure computed by multiplying the number of affected individuals by the number of years each individual is expected to live" – as defined by Commonwealth Department of Health and Ageing. (http://www.health.gov.au/)

listing.(510) However, George et al did not find an explicit cost-effectiveness ratio threshold beyond which the PBAC was unwilling to recommend PBS-listing for additional life-years gained. Therefore, the results of this study by George et al confirm that the PBAC considers factors other than economic efficiency when making decisions on PBS drug reimbursement. Even though the PBS has an uncapped budget, overall government resources allocated to health care are limited. Thus there is an opportunity cost associated with purchasing a particular 'medicine', in that resources allocated to one group of patients will be unavailable within the system to treat other patients. These are relevant and reasonable considerations, concordant with "accountability for reasonableness". The diligence of the PBAC to ensure wise, cost-effective use of public resources across the range of medical disciplines must be acknowledged. However, how PBAC deals with each of these dimensions (Table 7.3), particularly the societal ones, in individual decisions on drug subsidy is not communicated to clinicians and patients or publicly accessible. Further, to date there has been limited public discussion in Australia about these domains when attempting to decide on reasonable access criteria to HCMs. This task should be shared by all stakeholders in the National Medicines Policy. There is room for considerable improvement notwithstanding the population-policy environment and the contextual and legislative constraints under which PBS operates, and the already highly regarded performance and outcomes of the PBAC process.

7.2.4 The use of surrogate markers

Due to the very high cost of treatment for an individual patient in regards to HCMs, it is relevant and reasonable to monitor patient responses closely, and to withdraw treatment promptly if it is clear that the drug is ineffective. The PBS 'continuation

rule' for HCMs, including biologicals for RA, that requires regular assessment of disease activity is in accord with this notion, as described in this section. However, the basis for the 'effective' response criteria as incorporated in the access arrangements for HCMs for RA has not been explained.

RA patient response to biological agents is assessed objectively using inflammatory markers: blood concentrations of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The use of surrogate or intermediate outcomes, particularly laboratory tests, are relevant and reasonable thus concordant with "accountability for reasonableness" provided that they are valid and reliable measures of clinical and functional outcomes. CRP and ESR are commonly used blood markers of inflammation to evaluate RA disease activity in clinical practice and as indicators of treatment outcome.(511-514) For example, failure to suppress the plasma concentrations of CRP was a good indicator of failure to respond to infliximab therapy in RA patients.(515) Studies have also shown that elevated inflammatory activity as measured by inflammatory markers correlated with radiographic progression of joint damage.(516-518)

Clinically detectable inflammation often antedates structural damage of joints. A count of the number of swollen and tender joints is another quantitative clinical measure to assess and monitor the status of patients with RA.(519) The swollen joint count reflects inflammation of the synovial tissue and the tender joint count is associated more with the level of pain. Joint counts are a major component of response criteria used in RA clinical trials: for example, the disease activity score (DAS),(520, 521) the European League Against Rheumatism (EULAR) response criteria,(522) and the American College of Rheumatology (ACR) Core Data Set.(523)

Regular count of swollen and tender joints to assess disease activity in patients with RA is also recommended in clinical practice.(524) Thus, the use of a count of swollen and tender joints as a formal requirement of the PBS for access to biologicals is "relevant" and "reasonable".

Also useful for monitoring RA, but not required by the PBS, are global assessments of response, pain severity, and the extent of disability.(228, 525) In addition, radiographic progression of joint damage is a strong predictor and correlates with functional disability in the long-term and occurs early in the course of RA.(526) Controlling progressive joint damage is a key objective in the treatment of RA. Assessment of structural damage in RA is increasingly recognised as an important and relevant parameter in evaluating disease outcomes and progression,(527) although not a mandatory requirement of the PBS at this stage. Radiographs (including X-rays) are important tools for staging of RA as well as for ongoing monitoring. Further research is required to demonstrate the pharmacoeconomic importance of radiological progression. Access to, and continuation of, HCMs for RA is likely to incorporate this reasonable surrogate in the future.

Monitoring surrogate indicators for evidence of response to high-cost anti-rheumatic biologicals passes the "relevance" condition of "accountability for reasonableness". The main ethical issue here is how the decision about amounts of activity deemed to indicate a satisfactory response to biologicals in RA was reached. The PBS criteria require a demonstration of at least a 20% improvement from baseline in the CRP or ESR concentrations and a 50% reduction in the total number of joint count in order to gain continuing biological therapy (Chapter 2, Table 2.3). The evidence-base for these pre-determined quantifiable response criteria has not been publicised. The

concept of 'worthwhile' response to treatment would potentially benefit from wider stakeholder consultation when PBS response criteria are established.

7.2.5 Capacity to benefit

Likelihood of success (or capacity to benefit) is relevant from the perspective of distributive justice when the resource is not reusable,(38) and fits comfortably within the "accountability for reasonableness" framework. This is the case with high-cost drug treatments that require multiple doses, where the view that a scarce resource should be distributed to patients who have a reasonable chance of benefit is generally accepted. "Likely success" is interpreted in terms of maximising the probable benefit rather than in terms of probably maximising the benefit.(528) One eligibility criterion to allow access by RA patients to anti-rheumatic biologicals through the PBS was that patients must be, or have been, rheumatoid factor (RF) positive. This requirement raised particular concern as RF-negative RA can be as severe and debilitating as RF-positive RA. In order to understand the "relevance and reasonableness" of this decision, an examination was undertaken of the evidence for an association between RF-status and clinical response to tumour necrosis factor (TNF) inhibitors in patients with RA at the time the access criteria for TNF inhibitors was gazetted (2003). This examination and results are discussed in the following section.

7.2.6 Does rheumatoid-factor predict a response to TNF inhibitors in patients with RA?

A summary of this section has been published ("*Subsidised access to TNF-alpha inhibitors: is the rationale for exclusion of rheumatoid factor negative patients defensible?*" Med J Aust 2004; 181:457)

Rheumatoid factor (RF), discovered by Waaler in 1940, is not exclusively associated with RA. It is found in a number of other autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndrome, infectious diseases such as mycobacterium tuberculosis and Lyme disease, and has been detected in healthy people, increasing in prevalence with age.(529, 530) RF is a serologic criterion in the American College of Rheumatology classification criteria for RA.(531) However, its presence or absence is not definitive for a clinical diagnosis of RA, with RF being absent in approximately 30% of RA patients.(532) Studies suggest that patients who are RF-positive at baseline are more susceptible to persistent disease with development of erosions and functional disability.(533-537) The key question arises, therefore, as to whether RF-status can reasonably be justified as a reasonable and relevant eligibility criterion for access to biologicals? This would need to be based on: (i) its potential to predict and hence to target patients who are at risk of developing more severe forms of RA, and/or (ii) the predictive value for likelihood of response to TNF therapy. As the PBS criteria (apart from RF-status) based on joint counts, inflammatory markers and history of failure with DMARDs, already limited access to TNF inhibitors to patients with severe RA, using RF-positivity to predict and target patients who are at risk of developing severe RA, would not appear to be relevant. Thus, did RF-status predict likelihood of response to biological therapy?

7.2.6.1 Aims and objectives

The aim of this study was to examine the published literature for evidence of an association between RF-status and clinical response to TNF inhibitors in patients with RA at the time the PBS access criteria were announced (August 2003).

7.2.6.2 Methods

A review of the published studies was conducted. Clinical reviews of three TNF inhibitors in the treatment of RA, etanercept, infliximab and adalimumab were obtained from the United Sates Food and Drug Administration (FDA) web-site. An assessment report for etanercept and infliximab for RA was obtained from the United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) web-site. Searches were undertaken via the major databases 'Medline' (1966-January 2004) and 'PubMed' (performed February 2004). Searches were performed with the drug names (etanercept, infliximab, and adalimumab), limited to "clinical trials", which provided all types and phases of clinical trials of the three TNF inhibitors (PubMed: 132 papers, Medline: 203 papers). The data were scrutinised for their relevance to the subject of treating RA and whether response to treatment was assessed in relationship to the RF-status of the patients. Clinical trials were included and reviewed if any of the three TNF inhibitors were studied, as monotherapy or in combination with DMARDs. For adalimumab, published preliminary results of clinical trials were also reviewed. The application submitted by the sponsor of etanercept and relevant correspondence between the PBAC and the sponsor were also requested by the investigators.

7.2.6.3   Results

Information about the submitted application for PBS-listing and correspondence between the PBAC and the sponsor were not released by the sponsor.

Twenty one trials were reviewed, representing data on 5,963 subjects, including:

- Etanercept: 7 trials, 2,130 subjects (Table 7.4)

- Infliximab: 5 trials, 1,183 subjects (Table 7.5)

- Adalimumab: 9 trials, 2,612 subjects (Table 7.6)

RF-status of patients at baseline was recorded in most studies (16/21). The patient population in these studies was predominantly RF-positive (range: 59-88%).

Table 7.4 Clinical studies examining the efficacy of etanercept in patients with RA

First author (year)	Trial details	No. of subjects (n)	RF-positive subjects (%)
Moreland (1996) (538)	Phase I, toxicity and dose finding trial, 4-weeks duration	16	Not reported
Moreland (1997) (539)	Phase II, multicentre, randomised, double-blind, placebo-controlled trial, 3-months duration	180	Not reported
Weinblatt (1999) (540)	Phase II/III, Randomised, double-blind, placebo-controlled trial, 6-months duration	89	87
Moreland (1999) (229)	Phase III, multicentre, randomised, double-blind, placebo-controlled trial, 6-months duration	234	80
NICE (385)	European Etanercept Investigator Study: double-blind, 6-months duration	559	88
Bathon (2000) (458)	Randomised, double-blind, controlled trial (ERA trial), 12-months duration	632	88
Keystone (2004) (541)	Multicentre, randomised, double-blind, placebo-controlled trial, 16-weeks duration	420	59

NICE= National Institute for Health and Clinical Excellence

Table 7.5 Clinical trials examining the effects of infliximab in patients with RA

First author (year)	Trial details	No. of subjects (n)	RF-positive subjects (%)
Elliott (1994) (542)	Randomised double-blind, placebo-controlled trial, 4-weeks duration	73	81
Maini (1998) (419)	Double-blind, placebo-controlled, multicentre trial, 26-weeks duration	101	81
Maini (1999) (230)	Phase III trial – multicentre, placebo-controlled, double-blind, 12-months duration (ATTRACT trial)	428	81
Kavanaugh (2000) (543)	Pilot randomised, blinded trial, 3-months duration	28	82
Shergy (2002) (544)	Multicentre, open trial (PROMPT trial), 16-weeks duration	553	Not reported

Table 7.6 Clinical studies examining the efficacy of adalimumab in patients with RA

First author (year)	Trial details	No. of subjects (n)	RF-positive subjects (%)
den Broeder (2002) (545-547)	DE001/003, phase I, randomised, double-blind, placebo-controlled trial	120	83
Kempeni (546, 547)	DE004, phase I, randomised, double-blind, placebo-controlled trial	24	Not reported
Weisman (2003) (548)	DE005, phase I, randomized, double-blind, placebo-controlled, dose-titration study, 4-weeks duration	60	Not reported
van de Putte (2003) (549)	DE007, phase II, multicentre, placebo-controlled, double-blind trial, 12-weeks duration	284	84
Weinblatt (2003) (232)	DE009, phase II, multicentre, placebo-controlled, double-blind, dose-ranging trial (ARMADA trial), 24-weeks duration	271	79
Kempeni (546, 547)	DE010, phase I, randomised, double-blind, placebo-controlled trial	54	87
van de Putte (550, 551)	DE011, phase III, randomised, double-blind, placebo-controlled trial, 26-weeks duration	544	82
FDA (550)	DE019, phase III, multicentre, randomised, double-blind, placebo-controlled trial, 52-weeks duration	619	81
Furst (2003) (552)	DE031, phase III, multicentre, placebo-controlled, double-blind trial (STAR trial), 24-weeks duration	636	63

FDA= Food and Drug Administration

Subgroup analysis of patient response to treatment according to RF-status was not reported in any of the studies reviewed. The FDA clinical review of etanercept (553) included analyses of a phase III, randomised, placebo-controlled trial of 234 subjects by Moreland et al (year 1999). Conclusions of the FDA regarding the influences of RF-status on responses conflicted with those of the Manufacturer. The FDA carried out a logistic regression analysis to examine the influence of baseline variables. Of the baseline variables analysed, namely age, body surface area, weight, height, baseline RF-positivity, and study site, the FDA concluded that baseline RF-status was not predictive of a subject's likelihood of achieving an ACR20 response, the primary outcome measure of response. A higher tender joint count and a higher swollen joint count were weak predictors of achieving an ACR20 response.(553) The Manufacturer, in contrast, undertook a linear regression analysis of data and concluded that baseline RF-status was predictive of ACR20 responses to etanercept (the statistical significance was not reported). However, the FDA noted that the proportion of RF-negative subjects in each intervention group was small (approximately 20%), and that some RF-negative patients achieved high levels of clinical responses (namely, ACR50 and ACR70 responses) when treated with etanercept.(553)

Interpretation of subgroup results is challenging. Subgroup analysis within a clinical trial is often used to generate or test an hypothesis about risk factors or treatment responses.(554) In general, subgroup analyses should be defined *a priori* i.e. in the protocol of the study, and justified on the basis of known potential heterogeneity of treatment effect due to biological mechanisms or in response to findings in previous studies.(555, 556) However, the subgroup analysis of predicting response to

etanercept treatment by RF-status was not explicitly predefined in the trial by Moreland et al.(229) In this example, the manufacturer's *post hoc* analysis was treated with appropriate scepticism by the FDA. Pooled analysis of several trials was not undertaken subsequently which suggests that important subgroup effects were not identified.

7.2.6.4 Discussion

The evidence supporting each of the criteria for access to an HCM is not always obvious or available to practising clinicians and their patients, and sometimes can appear to contradict the public domain evidence. How reasonable decisions are in the view of stakeholders outside the decision-making process, is largely influenced by the degree of transparency around that process (further discussed in Section 7.3). The example of the debate around 'rheumatoid-factor-positive-status' as an eligibility criterion for access to TNF inhibitors highlights that upholding the ethical principle of "accountability for reasonableness" of decisions becomes challenging when there is a lack of transparency.

A review of 21 clinical trials of TNF inhibitors available in the public domain at the time the access criteria were announced revealed that only one clinical study, the 'Early Rheumatoid Arthritis (ERA) trial of the effect of etanercept on radiographic progression in patients with early RA', had RF-positivity as an inclusion criterion. RF-negative patients were enrolled if there was evidence of bone erosions via radiographs.(458) However, the aim of this inclusion criterion was to enhance the detection of differences in the rate of development of erosions, rather than to suggest RF-negative patients would derive less benefit.

RF-positivity as a criterion for PBS-subsidised access to TNF inhibitors for RA suggests that there were some grounds for considering this subgroup would be less likely to respond. This was despite most pivotal studies not excluding RF-negative patients or analysing them as a subgroup as part of an *a priori* plan. Clearly, the difference in responses to TNF inhibitor treatment perceived to exist by the PBAC between RF-positive and RF-negative patients was considered to be important from a cost-effectiveness perspective. The PBAC must have considered that the size of this difference was significant. How was this decision arrived at by PBAC? Presumably the listing criteria proposed and data submitted by the sponsor or other considerations must have led to this decision. Alternatively, RF-positivity as a criterion for PBS-subsidised access to TNF inhibitors for RA might have been justified on the basis of the availability of limited data for RF-negative patients. In other words cost-effectiveness had not been demonstrated in this subgroup. The broad justification for an exclusion of a subgroup of this type is that reimbursement decisions should be evidence-based and, therefore, the absence of evidence of cost-effectiveness leads to a non-subsidy decision. However, the paucity of published literature in support of an association between RF-status and response to treatment with TNF inhibitors in patients with severe RA and the lack of 'external' insight into the rationale for the decision meant that rheumatologists could not provide an evidence-based justification to their RF-negative patients as to why they were excluded from subsidised access to effective drugs. Similarly, no evidence for an association between RF-status and response to DMARDs had been reported.(557) Additionally, the PBS 'continuation rule' was already in place to serve as a safeguard against ongoing subsidised treatment in non-responders, so there was little risk of a 'blow-out' from this sub-set of RA patients because if they failed to respond, high-cost biological therapy would be stopped. Thus, for RF-negative patients with severe RA unresponsive to DMARDs, based on publicly available

evidence, this requirement for a positive RF test was not "reasonable" at least in external perception. The "relevance" condition of the "accountability for reasonableness" ethical framework was thus breached. Not surprisingly this led to public dissatisfaction.

7.2.6.4.1 PBAC's decision in regards to RF-positivity

The requirement for RF-positivity was requested by the sponsor of etanercept (as later revealed by Sansom, current chairman of the PBAC), because RF-positivity was believed to be a "treatment-effect modifier".(266) The PBAC decision clearly was a result of the committee's reasonable attempt to 'target' access to the small sub-set of patients most severely-affected with definite RA based on their higher potential to respond, and failure to respond to other therapies. Limiting access to the subgroup of patients in whom cost-effectiveness has been demonstrated (namely, RF-positive patients) is also a strategy to prevent harm because the long-term safety and efficacy of biologicals are uncertain (a finding of the interview study reported in Chapter 3). This satisfies the ethical principle of nonmaleficence – the principle expressed by the Latin *'primum non nocere'*, which means 'above all, do no harm'.(38)

The PBAC based its decision on a statistical analysis of individual patient data from two published randomised trials,(229, 540) provided by the sponsor of etanercept.(558) This *post hoc* analysis indicated that being RF-positive was associated with a better response to etanercept treatment.(266) Efficacy in RF-negative patients was not clearly established because of the small number of such patients in these trials.(558) This interpretation of the data was supported by the sponsor of etanercept,(558) and by the small number of rheumatologists from the

rheumatology association who advised the PBAC about the proposed restrictions for access to the biologicals.(266) However, the wider rheumatology community was not privy to these 'in-confidence' data or the 'thinking' of these key stakeholders (namely, the PBAC, the sponsor, and the rheumatologists engaged in the process) in arriving at this decision about the need for RF-positivity. Due to the fact that the sponsor had withheld access to this critical information, the PBAC was not able to defend its decision (and, therefore, to satisfy the "accountability for reasonableness" test) because regulations at the time did not allow publication of detailed reasons or data to explain the rationale. Further, because infliximab and adalimumab attained PBS-listing on the basis of equivalent efficacy to etanercept, the same access criteria were applied to these TNF inhibitors. Clearly the apparent 'mismatch' between PBS criteria and the published literature would have been at least better understood, and thus possibly justified and accepted, if the rationale, and optimally, the evidence on which this was based had been publicly accessible. It is also an important principle that individuals engaged in stakeholder consultations should be accountable with respect to communicating the rationale behind decisions sufficiently to their constituencies, although it is currently challenging because 'commercial-in-confidence' restrictions apply to such 'communication' and applied in this example of etanercept. This example highlights the issue that lack of transparency was fundamental to the concerns expressed by clinicians and patients about this decision. The efforts made by the PBAC in recent years to better inform the community about its decisions is, therefore, very welcome and constructive (further discussed in Section 7.3).

It should be acknowledged that the PBAC fairly promptly recognised this issue (there were considerable expressions of concern from the public) and actions were taken to rectify the situation. However, the PBAC has very limited capacity to

demand submissions from the pharmaceutical industry sponsors. In this example of the RF-positivity controversy, submission by sponsors of additional, new evidence in support of a review of the RF eligibility criterion was encouraged publicly by the PBAC. Additional data and a submission for change of this criterion, perhaps influenced by the substantial publicity around this matter, were then provided by the sponsor of etanercept to the PBAC.(558) This criterion was removed as of June 2005 as an acknowledgement that the 'continuation rule' would cover the issue of patients with 'inadequate' response (Table 7.7). The PBAC is to be commended for its commitment to ameliorate problems such as this and its willingness to consider new and additional data. However, it should also be noted that controls on access to medicines directly impact on the health and quality of life of individual patients. Throughout the 22 months that the requirement for RF-positivity was operational and while waiting for additional data by the sponsor to be prepared, submitted and considered, patients who had severe RA and otherwise fulfilled the PBS eligibility criteria (except for RF-positivity) were excluded from subsidised, potentially effective biological treatment and were subject to uncertainty about their prospects of ever gaining subsidised-access. A relevant ethical concern is that there was and still is no formal mechanism for appeal against PBS decisions by patients and clinicians. Allowing opportunities for appeals against decisions is a condition to be satisfied by the "accountability for reasonableness" framework (further discussed in Section 7.4).

Table 7.7 PBAC's decision to remove RF-positivity (March 2005)

"*The PBAC recommended that the rheumatoid arthritis restriction be amended by removing any reference to rheumatoid factor. The PBAC noted that, overall, there is suggestive evidence of weak treatment effect modification by rheumatoid factor status. At worst, being RF-ve results in a treatment effect to bDMARDs in terms of ACR20 and ACR50 response rates, but may result in an inferior treatment effect in terms of these response rates compared with being RF+ve. However, in view of the continuation rules in place for PBS-subsidised use of the bDMARDs, the level of response required to receive repeat treatment is the same for RF-ve and RF+ve patients and the lower response rate thus become less of an issue.*"

7.2.6.4.2 Are there predictors of response to TNF inhibitors in RA?

This section explores the pursuit of even better predictors of response to anti-TNF therapies in the recent literature.

Biological agents are very expensive, and their long-term safety at the time of reimbursement decisions, as for all drugs, was and remains uncertain. Understanding which subgroups of patients are likely to respond to these drugs ("likelihood of success") is thus a relevant and reasonable consideration in priority setting because it has important implications for the costs and sustainability of public subsidy systems as well as for minimising the risks of adverse events. In trials of the biologicals, about 50-70% of patients achieved a 50% improvement according to the ACR response criteria, that is 30-50% of patients were non-responders, or partial responders.(427, 462, 463) A recent observational, longitudinal study, using data collected via the British Biologics Register (described in Section 4.5), analysed 2,879 patients with RA taking etanercept and infliximab in the UK with the aim of identifying the factors at baseline that were associated with a good clinical response to TNF inhibitors.(389) The response was assessed using the EULAR response criteria.(559) This study found that baseline disease characteristics, including age, disease duration, RF and the number of DMARDs a patient used previously, did not predict response to treatment with either etanercept or infliximab. The most disabled patients were less likely to respond. It is possible that those patients who have failed many DMARDs and are most disabled represent a subgroup of RA patients with highly resistant disease. It was also suggested that genetic differences may influence the patient response to anti-TNF therapies.(389)

Much work is underway to prospectively identify patients most likely to benefit from these agents with an increasing emphasis on pharmacogenomic approaches. Recent studies have focussed on polymorphisms in genes encoding TNF-alpha, TNF-alpha receptors, other cytokines, and the major histocompatibility complex region. There is some evidence to suggest that single nucleotide polymorphisms in these genes are significant in predicting response to anti-TNF therapies.(560) It has been known for sometime, for example, that the presence of a shared epitope on the hypervariable region of HLA-DRB1 is associated with RA and more severe disease.(561) Accumulating evidence suggests that gene polymorphisms (HLA-DRB1, TNF, and interleukin-10) may also be predictive of clinical responsiveness to both TNF inhibitors and DMARDs.(562-564) Factors that do predict serious disease with poor outcomes but with the ability to respond to biological therapies will assist the move towards making these drugs available more precisely to those at greatest risk, i.e. capacity to benefit. This approach seems to be ethically sound while enhancing the underlying principle of cost-effective use. The need to attend to the conditions of "accountability for reasonableness" namely relevance, publicity, appeals, and enforcement, must be emphasised again in the use of such an approach.

7.2.7 The place of pharmacogenetics in individualising therapy

Benefits of medicines may vary considerably between individuals. In addition, the course of a disease in any individual is generally uncertain. The basic premise underlying pharmacogenomics is that the information regarding an individual patient's genetic make-up can be used to identify the drug with the optimal efficacy-safety profile or predict dosing regimes to a degree for that patient, leading to individualised drug therapy. The complex issues around pharmacogenetics are beyond the scope of the present work. However, it should be recognised that the use of pharmacogenetic testing is likely to be increasingly "relevant" in priority setting decisions on healthcare resources. Some have raised concerns regarding the potential lack of equity that may result from such an approach to individualising treatments (565) while others suggest individualised therapy can result in increased efficiency without any loss of equity.(566) In some cases, individualisation on this basis could even result in a more equitable distribution of health gains by providing each person with therapy that maximises health gains. Besides ethical issues, there are also legal and psychosocial implications of genetic testing that need to be considered.(567-569)

Examples of drugs whose funding by the Australian government already requires individual genetic information include: trastuzumab for the treatment of breast cancer (HER2 gene testing); imatinib for patients with chronic myeloid leukaemia (expression of the Philadelphia chromosome or the transcript, bcr-abl tyrosine kinase); and gefitinib for patients with non-small cell lung cancer (activating mutation of the epidermal growth factor receptor gene in tumour biopsy). These examples are likely to be a harbinger of drugs subsidised on PBS that will require pharmacogenetic testing as a pre-requisite for access. Additionally, recent guidance

by the FDA on the collection of pharmacogenetic information,(570) together with the amount of data available in the public domain to analyse the merits of using a particular genetic test, is likely to increase interest in this approach as a criterion for access. The author is a co-author of an editorial about the approach of targeting access to highly specialised drugs on the basis of an individual's genetic make-up ("*Tailoring access to high cost, genetically targeted drugs*". Med J Aust 2005; 182:607-608).

7.2.8 Stakeholder participation and Accountability for reasonableness

Procedural justice and inclusive decision-making processes are fundamental to a sense of community and ownership.(571) The guiding idea behind the four conditions of "accountability for reasonableness" is public deliberation. Perceptions of the relevance of the decisions would vary depending on the position of the stakeholder. Thus, stakeholder participation contributes to the legitimacy and fairness of the decision-making process and the decisions made. This occurs through democratization of the decision-making process and acts as a form of proxy consent.(484) Stakeholder participation is likely to provide a broader range of relevant reasons and rationale, and provides a clearer and more effective mechanism through which transparency may be achieved.(484) While the public has been involved in decisions on health services from the 1990s,(48) there has been limited involvement by patients or the public in decisions around medicines in most countries to date.(572)

As previously described, the PBAC consists of clinicians from different medical specialties, pharmacists, health economists, and a consumer representative. It is important to note that there has been a consumer representative on the PBAC since

the late 1990s.(573) Such an approach enables a reasonably wide range of perspectives to be considered and incorporated. To this extent, the condition of "fair minded people" starts to be met. Another step in the direction of increasing stakeholder involvement was taken in Australia when a unique stakeholder collaboration occurred between the PBAC, sponsor companies, and a small group of rheumatologists (the Australian Rheumatology Association Therapeutics Committee) leading to the subsidy of the anti-rheumatic biologicals, as described in Chapter 2. Current Chairman of the PBAC, Professor Lloyd Sansom, has championed the view that stakeholders need to be more involved and take more responsibility in the whole process of PBS-listing and post-listing activities. Increasingly the PBAC interacts with the respective sponsor and also with representatives from the relevant medical specialties in order to be better informed and to gain acceptance of its decisions.(85, 219) Increasing involvement of medical specialists is sensible and generally in accordance with the basic principle that decisions about health care should not only be based on clinical trial level evidence but also integrated with clinical expertise,(498) that is, the 'relevance' of the decision is likely to be enhanced. Also the broader range of stakeholders play the role of "fair-minded" individuals, as described in the "relevance" condition of the "accountability for reasonableness" framework (Table 7.1).(484) It is also consistent with the "partnership" approach advocated in Australia's National Medicines Policy. Sufficient access to unbiased credible information upon which each stakeholder group can form informed opinions is critical. Stakeholder collaboration was crucial in establishing a unique arrangement that allows patients to switch between biological therapies under the PBS, as discussed in the following section.

7.2.8.1 Switching between biological agents

An important practical question for funding bodies, physicians and patients was whether it was effective and cost-effective to prescribe another biological agent if one such agent had already failed. This relevant and reasonable question arose because the four biologicals licensed for use in RA have different pharmacological properties. Etanercept, infliximab, and adalimumab all neutralise the action of TNF-alpha, however, the chemical structure, pharmacokinetic properties, and specific mechanisms of TNF inhibition are different. Etanercept is a human fusion protein consisting of two recombinant soluble TNF-alpha receptors that inhibit the activity of TNF-alpha and lymphotoxin-alpha. Infliximab is a chimeric monoclonal anti-TNF antibody. Adalimumab is a fully humanised monoclonal anti-TNF antibody. Anakinra has another mechanism of action; it is an interleukin-1 antagonist.

Australia's PBS was the first publicly-funded system that allowed the sequential prescribing of biologicals for treating RA, a welcome and proactive initiative of the PBS. Under the 'interchangeability rule' introduced on 1 December 2004, RA patients eligible for biological therapy were allowed to trial different TNF inhibitors (up to two anti-TNF agents) and anakinra without the need to re-qualify against the initial eligibility criteria. This satisfies the ethical criterion of beneficence.(38) The limited evidence, largely founded on observational studies, seemed to indicate that patients who failed to respond to one TNF inhibitor could respond to the other agent. Also there appeared to be no contraindication to using one TNF inhibitor for patients who had developed hypersensitivity to another, but there were no data indicating the cost-effectiveness of switching. Published clinical studies are summarised in Table 7.8, including recently published studies (i.e. post "interchangeability rule").

Table 7.8 Overview of published studies examined switching between biologicals

First author (year)	Drugs	Number of patients	Main finding
Brocq (2002) (574)	Etanercept, infliximab	14	Etanercept or infliximab treatment was stopped because of adverse events or inefficacy. Patients benefited from switching to the other agent
Ang (2003) (575)	Etanercept, infliximab	29	Patients who fail to respond to one TNF inhibitor can respond to the other antagonists
Van Vollenhoven (2003) (404)	Etanercept, infliximab	31	For patients with insufficient efficacy from etanercept (or adverse events from infliximab), treatment with infliximab (or etanercept) provided a safe and effective treatment alternative
Gomez-Puerta (2004) (576, 577)	Etanercept, infliximab	12	Patients who were switched from infliximab to etanercept responded well without serious adverse events
Hansen (2004) (578)	Etanercept, infliximab	20	Lack of response to one agent did not predict a lack of response to another
Haraoui (2004) (579)	Etanercept, infliximab	25	Etanercept is a safe and effective treatment option for patients in whom infliximab was ineffective
Favalli (2004) (580)	Etanercept, infliximab	15 (7 patients had juvenile chronic arthritis)	For patients with insufficient efficacy or adverse events from etanercept (or infliximab), treatment with infliximab (or etanercept) provided a safe and effective treatment alternative
Yazici (2004) (581)	Etanercept, infliximab	20	Better response to infliximab in etanercept-naïve patients
Wick (2005) (582)	Adalimumab, etanercept, infliximab	36	Adalimumab is effective in patients who have failed etanercept or infliximab
Cohen (2005) (583)	Etanercept, infliximab	38	Switching between TNF inhibitors is sensible, regardless of which agent was used first
Bennett (2005) (584)	Etanercept, infliximab, adalimumab, anakinra	26	Adalimumab is effective in patients with previous biological failures
Nikas (2006) (585)	Adalimumab, infliximab	24	Adalimumab is effective in patients who have discontinued infliximab
Gomez-Reino (2006) (374)	Etanercept, infliximab, adalimumab	488 patients with chronic arthropathies	Results support the use of a different TNF inhibitor in patients who have failed to respond to a TNF inhibitor

Although these studies lacked the protection a RCT provides against bias and the numbers of patients studied was quite small, at the time the decision to allow 'sequential' biological prescribing was made, this was enough evidence for the PBAC to recommend that anti-TNF therapy should not be abandoned following an apparent, initially unsatisfactory response to a specific TNF inhibitor. In addition, stakeholder involvement was crucial in achieving this timely modification to the access arrangements for anti-rheumatic biologicals, a finding of the interview study undertaken as part of this work. There was stakeholder participation in ongoing discussions about the logistics of sequential use of biological agents between the PBAC, sponsors, and a number of rheumatologists after initial PBS-listing of etanercept (Chapter 3). Clearly this helpful decision by the PBAC demonstrates a level of flexibility in PBS decision-making and the effect of stakeholder collaboration in action: that is, a reasonable and relevant rationale (namely, contextual considerations, supporting evidence from observational studies and clinical advice by participating rheumatologists), rather than evidence solely from RCTs, could be influential in PBS reaching decisions. On ethical examination this decision scores well against "accountability for reasonableness". Also, this example from the PBS system demonstrates accountability as eligible patients should benefit clinically from this decision. Further, the proactive stance of PBAC meant that there was no hiatus between the first patients failing treatment with etanercept and an option for them to move easily to treatment with an alternate biological agent. On the experience so far, and from the ethical analysis of the PBS system, it seems sensible that the stakeholder consultation process should be supported and further developed beyond its promising infancy. First steps might focus on gaining a better understanding of the possible influences on stakeholder perceptions of the value of a particular therapy, establishing mechanisms to ensure sufficient access to unbiased, good quality information upon which each stakeholder group can form

informed opinions, achieving more direct consumer involvement, and the consultation process becoming more open and structured, as described in the next section.

7.2.8.2   *Direct consumer involvement in the PBS process*

Stakeholder consultation has been an innovative change to the PBS-listing process, as noted. Whilst such innovation is welcome, the process of consumer engagement needs to be more fully developed if the ideals of the "accountability for reasonableness" and the National Medicines Policy frameworks are to be achieved. Clearly, there is considerable room for improvement in communication and interaction with clinician and patient groups in order to be able to describe the PBS decision-making process as transparent and truly inclusive. Stakeholders' access to this process, particularly for patient and consumer groups, appears to be reactive to date, *ad hoc* and quite limited in scope. Increased participation by consumer representatives and patients in PBAC processes of establishing access criteria for HCMs was identified as an important need and goal in the interview study carried out as part of this research (Chapter 3). Patient and community involvement in decision-making is a multidimensional process and complex and, therefore, requires careful exploration to address issues around needs, roles, responsibilities, resources, decision-making processes, beneficiaries, consequences,(586) and, importantly, education so that consumers can form informed opinions. The potential influence of the industry must be recognised and disclosure of conflicts of interest from participants in decision-making processes is crucial. Recently the Consumers Health Forum and Medicines Australia co-sponsored work towards a manual to guide consumer organisations in their interactions with the pharmaceutical industry.(269) Consumer input can supplement clinical and economic considerations,

as well as enhancing accountability and openness of the decision-making process and the decisions actually made.(587) Thus, the "accountability for reasonableness" ethical framework and the National Medicines Policy indicate the importance of consumer involvement and ownership of PBAC decisions.

The most notable model of a deliberative mechanism developed involving consumers in decisions around healthcare is that of the National Institute for Health and Clinical Excellence (NICE) in the UK. Patients and the public have played an active and successful role in all aspects of decision-making, including the consultation process about new medicines and technologies, and the development of lay versions of all NICE materials through a Patient Involvement Unit.(588) The Citizens' Council, representing the population of the UK, provides advice in response to specific questions to NICE such that societal views about all key decisions are considered.(572) This model is clearly aligned with "accountability for reasonableness" that emphasises democratic deliberation.

The approach of Citizen's juries has recently been trialed in Western Australia as a means to introduce greater democracy into the decision-making process of priority setting in healthcare.(589) It was found that Citizen's juries were capable of dealing with complex concepts such as "equity" and of providing meaningful input on issues regarding healthcare resource allocation.(589)

Participants engaged during decision-making processes potentially influence the final decisions made.(507) Power differences exist when the interests of some individuals and groups dominate and/or are better positioned than others to influence decisions.(284) Gibson et al proposed "empowerment" as an additional

element to the "accountability for reasonableness" framework. Empowerment requires that there should be efforts to minimise power differences in the decision-making process and to optimise effective opportunities for participation in decision-making.(284) The qualitative research reported in this thesis found that power differences existed in the decision-making process for PBS-listing of biologicals. The rheumatologists, for example, were described as "relatively inexperienced" in such processes (Chapter 3). The example of the RF-positivity requirement for access to TNF inhibitors suggests that there were power differences between the stakeholders. Whilst a welcome move that stakeholders are increasingly involved in PBAC decisions, education and hence empowerment of all participating stakeholders is essential to optimise their contribution to decision-making and more importantly, to satisfy the ethical framework upon which the PBS should be based.

It is a challenge to ensure that stakeholder involvement does not impair the PBAC and similar formulary committees from making difficult and timely decisions to ensure scarce societal resources are used wisely. However, if patients and the public are not involved, the increasingly difficult decisions that must be made by PBAC and similar committees will be seen as illegitimate, and rightly so. Undoubtedly, the PBAC bears final and legislative responsibility for the decisions on reimbursement and access criteria for medicines on the PBS, but all stakeholders (patients, physicians, government, health policy and medical experts, industry, and research organisations) should share in the decision-making process. Such a process clearly would be concordant with "accountability for reasonableness" and Australia's National Medicines Policy.

7.3 Publicity (Transparency)

For the "publicity" condition, or more commonly termed "transparency" in Australia, the public should have access to the rationale and evidence behind decisions being made (Table 7.1). According to Daniels and Sabin, transparency around the grounds for decisions improves the quality of the decision-making, and openness improves public understanding of the necessity for priority decisions and promotes a culture of education and learning between stakeholders.(484) Sabin has encapsulated this view well: "unless the reasons for non-coverage policy are articulated there is no opportunity for debate, focused criticism and societal learning".(590) Transparency is necessary for accountability and reduces controversy around decisions, so that the decision-making process and the final decisions are seen to be legitimate. External transparency would be considered to be present if the process, deliberations, decisions and reasoning behind the decision-making were available to stakeholders external to the membership of the decision-making committees,(67) i.e. accessible by people both inside and outside of the PBS assessment process. This would increase the level of confidence and support that the public has for the entity, the process and the decisions.(591)

At times the PBS criteria for access to a medicine appear contrary to published literature, as illustrated by the example of the requirement for RF-positivity in RA (Section 7.2.6). Another example was the requirement for a positive HLA-B27 as part of PBS criteria for use of TNF inhibitors to treat ankylosing spondylitis. Smith and Ahern observed that the requirement for a positive HLA-B27 was not supported by the published evidence.(592) How then was this decision reached? Again, in this example, sponsor-proposed access criteria for TNF inhibitors for ankylosing spondylitis, submitted data, economic evaluations, PBAC deliberations and

considerations were not available to those outside the PBS/PBAC assessment process, thus breaching the condition of "transparency" in "accountability for reasonableness". These examples indicate at least a lack of understanding of the basis for the original PBS decisions that were said to be 'evidence-based'. The evidence available in the public domain at the time did not lead to the same conclusions. In such circumstances, the decisions appeared "not relevant" at least in the view of stakeholders outside the decision-making process and concerns were aroused regarding the rationale behind such decisions. This reduces confidence in and support for the PBS and the PBAC. The requirement for HLA-B27 positivity has recently been removed by the PBAC (July 2006).

The transparency around the PBS system and PBAC decisions has increased dramatically, particularly over the last few years, aligning more closely with "accountability for reasonableness". The PBAC membership was not made public until 1973.(573) A case study by Cookson in 2000 examining the use of economic analysis in PBS decisions found that despite being considered a success by stakeholders, there were several criticisms about the decision-making process. These criticisms included the methodology, transparency and accountability. Findings from the interviews showed that some considered that the process lacked transparency, there was no consumer involvement in the design of the mandatory use of economic evaluation ("fourth hurdle") and there was insufficient consideration of equity.(593) These observations have been dealt with to a degree since 2000 in the PBS system.

Leading members and representatives of different medical specialties increasingly have been invited to attend PBAC meetings as observers in recent years in the quest to enhance transparency. An additional purpose has been to enhance clinicians' understanding of the PBAC process, the PBS system and, particularly, the constraints and difficulties involved. Also attending as observers at PBAC meetings have been staff from the National Prescribing Service, an independent organisation funded by the Commonwealth Department of Health and Ageing in supporting the Quality Use of Medicines (described in Chapter 1).(119) In November 2003, Rational Assessment of Drugs and Research (RADAR), was commenced by the National Prescribing Service to provide timely, independent, evidence-based information on new drugs and related PBS-listing information to health professionals. This is valuable and the National Prescribing Service is an increasingly important influence on the quality of prescribing and therapeutics in Australia. One stakeholder group characteristically overlooked in this initiative is the consumer/patient sector, an oversight that needs to be rectified.

In 2001, the Department of Health and Ageing started publishing on its web-site a quarterly summary of the PBAC's positive recommendations, with a brief summary of the basis on which each approval was made. Although welcomed as a positive move, Lopert and Henry suggested that the information on those medicines that had been rejected and the grounds for these rejections should also be available in the public domain.(204, 594) Subsequently, from June 2003, all recommendations of the PBAC to list, not list or defer a decision to list a medicine on the PBS have been made publicly available on the Department's web-site. Clearly, Australia can achieve greater transparency on its own initiative, without the influence of the Australia-United States Free Trade Agreement (AUSFTA). In particular, the negotiations of AUSFTA emphasised the need to support "pharmaceutical innovation" but

consumers' need for equitable and affordable access to essential medicines was not equally acknowledged.(595, 596)

In 2004, Sansom (the current chairman of the PBAC) stated that the need for greater understanding and transparency of the process is essential.(85) However, limitations to full and open disclosure of reasons for decisions were acknowledged.(85) The PBAC used the establishment of the AUSFTA as an opportunity to increase transparency and as a consequence, the PBAC is now able to release much more information about how it reaches its decisions and how the data is reviewed. Following negotiation between PBAC and industry, Public Summary Documents (Table 7.9) relating to PBAC decisions are published on the Department's web-site from November 2005, representing significant improvement in the transparency around PBAC decisions. This is a very important milestone for the PBS and continues an initiative for greater transparency driven by Sansom, the chairman of the PBAC.(597) These summary documents now provide an outline of submissions made and some justification of the rationale behind PBAC decisions. Although 'commercial-in-confidence' data remains unpublished, increasingly explicit summaries of this content are available in the Public Summary Documents. Community concerns would have been reduced markedly if relevant 'Public Summary Documents' existed at the time when positive RF and HLA-B27 tests were elements of the access criteria for TNF inhibitors.

Table 7.9 Details contained in Public Summary Documents

- Product and sponsor
- Date of PBAC consideration
- Purpose of application
- Background (e.g. the product is already subsidised by the PBS for another indication, or previously considered by the PBAC etc)
- Registration status
- Listing requested and PBAC's view
- Clinical place for the proposed therapy
- Comparator
- Clinical trials and results of trials
- Clinical claim
- Brief information about the economic analysis undertaken
- Estimated PBS usage and financial implications
- Recommendation and reasons
- Context for decision
- Sponsor's comment

An important aspect of PBAC decisions is the influence or weight placed on the contextual analysis (Table 7.3, Section 7.2.3). This aspect of decisions remains relatively opaque to clinicians and patients outside the PBS process. Greater transparency around the weighting placed on each of the domains, how the domains are dealt with, and how decisions are influenced by these considerations is critical. A suggestion is to address the list of considered dimensions (Table 7.3) in the Public Summary Documents pertaining to specific PBAC decisions, the value of the Public Summary Documents would also be further enhanced. This step forward is likely to lead to stronger support and appreciation of PBS and its decisions by the broader therapeutic community, thus enhancing compliance with access criteria.

Despite improvements towards greater transparency mentioned above, there is a still a difference between the 'evidence' reviewed by PBAC and that accessible by clinicians and consumers, and this can be critical to understanding the PBAC decisions. Major submissions by sponsors include published literature as well as unpublished data held by them on the new product and a comparator drug to enable

evaluation of the comparative clinical- and cost-effectiveness (Table 7.2).(85, 187) Under the AUSFTA, transparency relating to the PBS was promoted by the pharmaceutical industry.(596) However, while recent efforts have been made by the PBAC to increase transparency (as noted), the "commercial-in-confidence" right of the industry continued under the AUSFTA.(595) Pharmaceutical companies remain hesitant to publicly release all the information they have submitted to the PBAC to date.(598, 599) These evaluations containing comparative analyses are critical not only for justifying the legitimacy and fairness of PBAC decisions but also for informing clinicians and patients about the appropriate, safe, effective and cost-effective use of the new drug in clinical practice. As emphasised by Daniels et al and pertinent to this point, decision-making (*and justification*) should be publicly accessible in a system that supports democratic procedures.(492) Publishing economic analyses submitted to government authorities and disclosing potential conflicts of interest would be critical steps in the quest to achieve full transparency. Further contributions by both the industry and PBAC, in particular the industry, towards full transparency regarding PBAC decisions are still needed for achieving "accountability for reasonableness" of the PBS.

In summary, full transparency around PBAC decisions including the clinical- and cost-effectiveness evidence used and analysed, the requested criteria for access, details about the stakeholders involved and consultations with them, the contextual analysis and the weighting placed on each of the contextual domains is a critical and necessary step to align PBAC processes and decisions closer with the "accountability for reasonableness" and National Medicines Policy frameworks. Representatives engaged in the stakeholder collaboration processes have an important role and are accountable for communicating the rationale of PBAC decisions to clinicians and patients. It is essential that this obligation continue even as broader transparency is

achieved. Some of the PBS-criteria for biologicals were seen as contentious because the rationale for these decisions was not transparent and not communicated sufficiently. Together with greater transparency, increased accountability and better communication are fundamental for public understanding and support.

7.4   Appeals (Revision)

"Accountability for reasonableness" requires that formal mechanisms be established so that disputes might be better resolved, as well as providing opportunities to revisit and revise decisions in light of further evidence (Table 7.1). Moreover, this "appeals" condition also requires that procedures for tabling fair grievance be in place as a route for patients and their families to voice concerns, not necessarily for a reconsideration of the original decision.(56)

There is a paucity of research on priority setting processes around new technologies/medicines at a national, governmental level, as noted previously. A study on a priority setting process in a hospital in Canada, although a different healthcare setting, found that an established appeals process was a fundamental component to overall perceived fairness of the decision-making process.(600) It also allowed for an even more inclusive stakeholder process (allow participation from individuals who may not have been involved in the original decision-making process) and increased overall stakeholder satisfaction.(600)

In the Australian context, the recent establishment of an independent review mechanism as part of the AUSFTA that enable sponsors to seek a review of a negative PBAC decision (85) is concordant with the appeals condition of "accountability for reasonableness". However, access of other stakeholders to this mechanism is not available.

Further, there is no established mechanism for public input or appeals against draft and final PBS restrictions on prescribing following a positive PBAC recommendation on listing. In the examples of RF and HLA-B27 tests, delays in modifications to access criteria were ethically concerning. When and whether changes (or "updates") in PBS criteria for access to a medicine occur or not appears to be a somewhat '*ad hoc*' matter. Unless there is a defined process, this introduces the possibility of 'uneven' alterations depending on the size, enthusiasm, resources, or political influence of the stakeholder groups involved. In addition, as noted the PBS system is constrained by its reliance on applications from sponsors for listing and access criteria when other stakeholders' views and priorities might differ in terms of outcomes for sub-sets of patients not included in the proposed access criteria. "Accountability for reasonableness" and the National Medicines Policy direct that all stakeholders should have access to appeal mechanisms around PBAC decisions at a central decision level, this is a critical gap in the system yet to be filled.

7.5 Enforcement

The "accountability for reasonableness" framework also requires that there be voluntary or public regulation of the process to ensure that the other three conditions (relevance, transparency, and appeals of decisions) are met (Table 7.1), that is, a mechanism to hold decision makers accountable. The PBS is a public scheme with

accountability structure as governed by the Australian *National Health Act 1953* and the *National Health (Pharmaceutical Benefits) Regulations 1960*. This legislative framework serves as a form of regulation, and at times, the PBS is audited by the Australian National Audit Office.(601) Additionally, some degree of voluntary enforcement has also been present in the system in recent years through the involvement of stakeholders (Section 7.2.8). Access to HCMs via the PBS is carefully implemented by Medicare Australia. Medicare Australia is governed by the *Financial Management and Accountability Act 1997* and the *Public Service Act 1999*. Medicare Australia is within the Department of Human Services and is audited by the Australian National Audit Office regularly (http://www.medicareaustralia.gov.au/). These are some "enforcement" to ensure a legitimate and fair decision-making and implementation processes.

Evaluation is demanded by the National Medicines Policy and Quality Use of Medicines frameworks and is particularly important for an effective "enforcement" condition of the "accountability for reasonableness" framework. The PBS-listing process and PBS decisions, although under intense public scrutiny, are not subject to regular evaluation to assure accountability. Qualitative methods for investigating stakeholder perceptions and quantitative evaluation of drug utilisation and health outcomes are both essential. Drug Utilisation Sub-Committee advises the PBAC on patterns and changes of drug use associated with PBS-listing restrictions, however, there is minimal evaluation of health outcomes. Criteria for access to medicines should be accompanied by a rigorous assessment of the impact of the decisions (i.e. PBS restrictions) coupled with constant review of these restrictions in light of evidence derived from evaluations and the continuously evolving scientific evidence. A proactive monitoring system will need to be formally established to enable such post-subsidy evaluations and continuous review (Chapter 4). Current restrictions on

data linkage and difficult access to individual-level data for analysing drug utilisation and health outcomes are some major barriers to post-subsidy evaluation (described in Chapter 4). Given the size of the expenditure on HCMs, for example, anti-rheumatic biologicals and the consequences of treatment, or withholding of treatment, the collection and analysis of data pertinent to the use of these drugs could be considered an ethical necessity. Further, analysis of outcomes of the Australian patient population accessing biologicals is critical for the accountability of the PBS, particularly because the PBS-criteria target a more severely-diseased RA patient sub-set than patients accessing biologicals in other countries (Section 4.5) and those patients included in the pivotal RCTs used by the PBAC to decide on access criteria. This seems extremely hard to justify given the huge investment in PBS medicines and the purported standard of accountability for the PBS and its decisions.

7.6 The example of the decision-making process of the National Institute for Health and Clinical Excellence

The stakeholder consultation process has been an innovation in Australia, first applied to the subsidy of anti-rheumatic biologicals. To advance this important development locally, lessons from other countries with established stakeholder engagement are potentially invaluable. The decision-making process followed by NICE is particularly commendable for its openness, transparency, the opportunity for and the range of stakeholders involved, and its commitment to the use of the best available evidence.(602) The healthcare priority setting in the UK has been criticised, however. In particular, the opaque and obscure selection of technologies and medicines by the Department of Health for NICE to review,(108) the use of manufacturers' commercial-in-confidence evidence conflicts NICE's goal of

transparency, the lack of advice about local funding,(603) and the variable implementation of NICE guidelines across the UK,(128) have been singled out for attention. Despite these criticisms, the NICE review process itself is on the whole aligned with the "accountability for reasonableness" framework. Investigators of a recent qualitative study examining centralised drug review processes from the view of decision makers also concluded that the NICE process in the UK had made the greatest efforts towards meeting the "transparency" condition when compared to that of Canada, Australia, and New Zealand.(604) Thus, NICE provides a good example for Australia and other countries to follow with respect to the details of deliberations and decisions that could be made available in the public domain (i.e. transparency) and the extensive involvement of stakeholders in the decision-making processes. A summary of the NICE process now follows (Figure 7.1).(605-607)

For each review of the clinical- and cost-effectiveness of medicines (termed "appraisal"), consumer and health professional organisations nominate their own experts to inform the Appraisal Committee advising NICE. An independent academic centre is commissioned to prepare an independent and systematic review of both the published evidence and any data submitted by the industry sponsor(s), thus the evidence-based decision-making capacity is enhanced. An Assessment Report by the academic group (unpublished data from industry is removed) is published on the NICE web-site. Stakeholders consulted in the process are explicitly identified (such as patient organisations, healthcare professional organisations, and the pharmaceutical industry related to the medicine), and are invited to submit comments about what issues should be considered in the appraisal (Figure 7.1).(605, 606) The 'Patient and Public Involving Program' provides training and support for individual patients, carers, and the public so that they can be appropriately involved in the NICE decision-making process.(608) This is a critically

important aspect of the NICE process. Assessment reports and submissions from stakeholders are considered by the Appraisal committee, producing an Appraisal Consultation Document; this document and meeting minutes are made publicly available, although a criticism is that the presentation style of cost-effectiveness studies was less than clear for non-economists and needs to be improved.(609) Stakeholders are able to comment on the consultation document and assessment report over a four-week period. The appraisal committee considers any feedback from consultants and comments via the web-site and produces final recommendations that are submitted to NICE. On average, the appraisal process takes about 12 months.(607) Furthermore, mechanisms exist for revision of and appeals against NICE decisions. Appeals can be made against the final recommendations before they are issued as 'NICE guidance' (Figure 7.1). NICE guidance is reviewed; a review date is set after consultation in order to accommodate major new evidence.(607) The NICE guidance on drugs for Alzheimer's disease is an example illustrating revision and appeals in action: NICE's original guidance was recently revised, and appeals against its original decision were taken into consideration in the process.(610) It is apparent that overall the conditions of the ethical framework "accountability for reasonableness" grounded in procedural justice and emphasises democratic deliberation, as noted previously, have been dealt with satisfactorily by NICE.
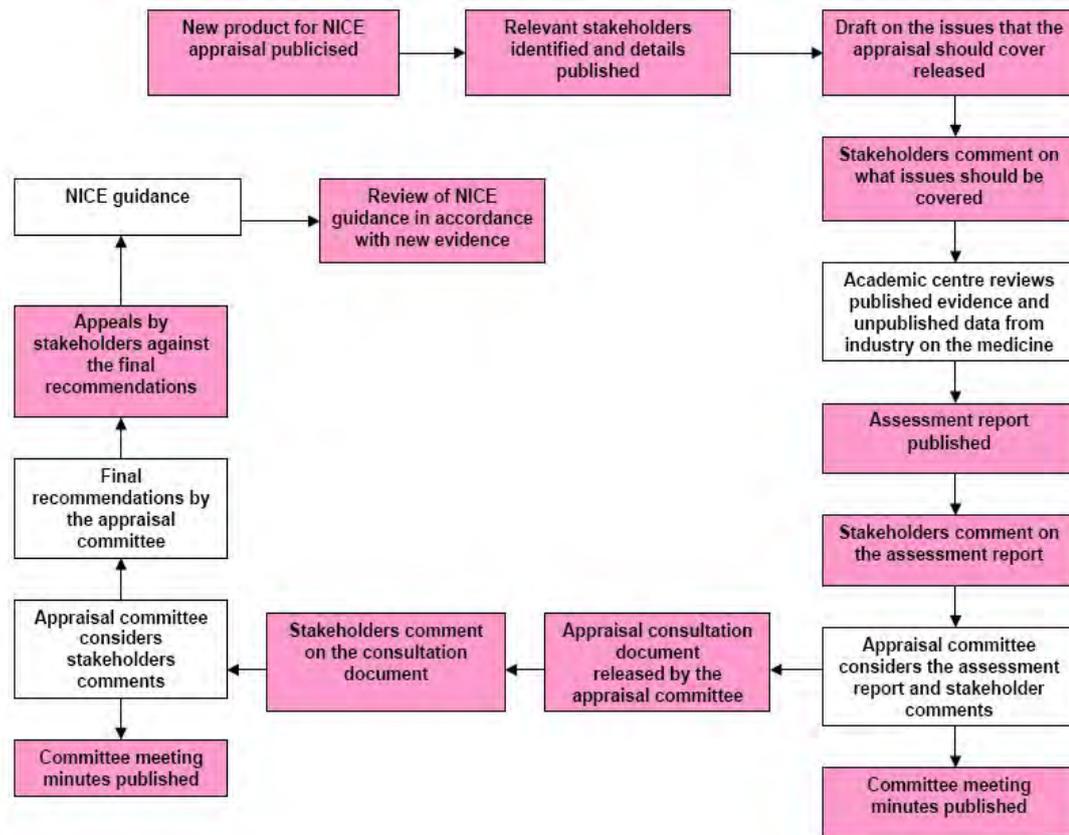
Figure 7.1 The NICE appraisal process in the UK

Using the NICE process map as the example, possible enhancements in the PBAC decision-making process critical for strengthening the legitimacy, fairness and thus, "accountability for reasonableness" of PBS decisions are colour-highlighted in Figure 7.1. In order to attain comparability with NICE in regards to transparency and accountability, the proposed areas for possible improvement in the PBS process include: (i) all PBS-listing evaluations, deliberations and consultations be publicly accessible; (ii) making stakeholder involvement mandatory for submissions on HCMs (at least) since access is often targeted to a smaller sub-set of the patient population with a disease; (iii) much greater inclusion of consumers and patients in the processes; (iv) establish mechanisms for appeals and revision of decisions; (v) making draft PBS restrictions available and accessible in the public domain so enabling stakeholders to comment within a reasonable timeframe before

implementation, and (vi) developing explicit criteria for the balance between scientific evidence and the ethical and social value judgements when assessing a new medicine (this was also a suggested area for improvement in the NICE process (602)). These are major and crucial steps worthy of consideration and would strengthen public confidence in PBS decisions.

7.7 Implementing the PBS restrictions and ethics

The pivotal goal of fairness has been described as including equity, efficiency, and accountability.(611) On the surface, objective PBS eligibility criteria for access to HCMs appear to be an impartial approach that maximises benefits from these therapies within acceptable norms of public policy. However, there are some areas that need attention with respect to the implementation of PBS restrictions for governing access to anti-rheumatic biologicals; these are highlighted in this section.

A basic requirement of justice is that "equals must be treated equally, and unequals must be treated unequally" – Aristotle. Equal access for equal need requires that those with equal needs have equal opportunities to access care ('horizontal equity'); and those with unequal needs have appropriately unequal opportunities to access care ('vertical equity').(612) The priority scheme set by the PBS-criteria should be fair on the basis that judgments about factors that are exogenous to the health of individuals who are already ill are not involved. However, patients with equal needs do not necessarily have equal opportunities to access specialist services in Australia. Access to a rheumatologist varies considerably between the States and Territories and the PBS-criteria require a rheumatologist to apply for the biologicals on behalf of a patient. Analysis of prescription data by geographical location indicates, not surprisingly, that there is a correlation between utilisation of biologicals and the *per*

capita ratio of rheumatologists (Chapter 5). Patients in remote or rural areas are thus disadvantaged by this criterion. Other factors potentially influence an individual's behaviour in seeking specialist care include income, indirect costs (e.g. travel costs, foregone wages), access to information, and cultural beliefs (thus willingness to access healthcare). Variations in the supply of healthcare, especially specialist services, are extant and should be acknowledged because healthcare cannot be allocated entirely equally across all areas.(428) Nevertheless, a remedy is needed as the goal of fairness is not being achieved. Geographical impediments to legitimate access could be overcome, for example, by allowing general physicians in remote and rural areas to apply for access to HCMs (e.g. anti-rheumatic biologicals) for their patients.

'Authority required' prescribing and detailed patient eligibility for access to anti-rheumatic biologicals may have largely prevented prescribing outside of the PBS-approved indication and criteria for access. This practice, sometimes known as 'leakage', has been documented with other PBS-subsidised medicines in Australia.(137) However, the administrative procedures to be followed for access to high-cost biologicals are time-consuming for prescribers and patients where much information is requested by Medicare Australia. There have been reports of difficulty locating records of laboratory tests and detailed pharmacotherapy histories for many patients. This problem is likely to diminish as patients with shorter histories of rheumatoid arthritis become eligible for these medicines. For prescribers, however, these requirements are often seen to be intrusive, and a means of 'policing' inappropriate or over-use (Chapter 3). Additional administrative procedures are likely to reduce the amount of time physicians have to interact with their patients. Administrative burden is an issue that has also been identified by pharmaceutical benefit management organisations in the United States.(161) Such procedures are

also administratively cumbersome and costly for the PBS (Chapter 3), thus reducing administrative efficiency – a goal of fairness as noted. Resources may be better spent on evaluation of the access scheme, audit and feedback to prescribers, and education of clinicians and consumers. The best use of these substantial resources should be carefully considered during decision-making in light of the goals of the PBS and again, the "accountability of reasonableness" ethical framework.

Under the ethical principle of "accountability", prescribers and patients accessing public resources have an obligation, both clinically and ethically, to monitor the effects of all medicines and be prepared to withdraw therapy if there is inadequate response. Clinicians have a responsibility to provide optimal care, but to do so within the boundaries of the system (i.e. without 'fudging' measures), so that equity of access for all patients is preserved.(613) Generally, it is a good concept that there should be agreement about what constitutes an acceptable response to drug therapy prior to commencement, whether treatment is subsidised or not.

Providing the public with balanced and sufficient information is consistent with the "accountability for reasonableness" and the Quality Use of Medicines frameworks. The approach of a "patient agreement" that treatment will only continue if there is a satisfactory response has been increasingly used by the PBS, including the anti-rheumatic biological treatments. However, the briefness of the written explanation for this agreement contained in the *Patient Acknowledgement Form* was and still is an ethical concern. Further, the principle of individual autonomy was not satisfactorily dealt with in this example. It is clear that the patient has a right to be informed about controls on access, and why the medicine is only subsidised under certain restrictions.(597) Due to the complexity of the PBS-criteria, costs and

potential risks of toxicity of biologicals, a brief but educational information sheet appears necessary to improve understanding of the issues important to a patient who may be seeking subsidised treatment. The clinician's role is also critical in helping the patient come to a reasonable decision given their circumstances, the evidence for effectiveness and safety, and any caveats to ongoing access such as the 'continuation rule'. More fulsome explanatory material or guidance to clinicians regarding how to address this novel 'continuation rule' with patients is clearly needed. Efforts by the PBS to communicate this type of information as Public Summary Documents are welcome. However, clearly much more effort is needed to enhance the accountability of the PBS, particularly information for patients about constraints on access to subsidised treatments will be a helpful background to assure community confidence.

7.8 Way forward: A formal appeal mechanism

Clearly the PBS system is largely ethically based, although an explicit ethical framework has not been the basis on which our national approach has been built. This analysis suggests that using an ethical framework and analysis would be productive as we move towards even more challenging times trying to balance demand with resources. There is substantial value in incorporating ethical considerations into the process and system for developing and improving our access to HCMs through the PBS and similar systems and any other approach is much more likely to encounter difficulties.

The major challenge in "priority setting" is to balance the tension between meeting both the needs of the individual and the community in a responsible and ethical way. Australia's National Medicines Policy recognises the significance of achieving this

balance. As described previously, the PBAC operates in a decision-making context that involves clinical as well as broader social, economic, and political factors. The PBAC has a very challenging but vital task that it undertakes with skill and dedication. However, at times there are apparent inconsistencies between the PBS criteria for patient access to medicines and the published literature as has been illustrated with the TNF inhibitors for treating rheumatic conditions (Section 7.2.6); the PBAC's commitment to ameliorate public concerns should be acknowledged. Need for and likelihood of success with a therapy are both value-laden concepts commonly reflecting clinical judgment. These concepts can and are applied at the population and individual patient level and herein lies the origin of much of the tension around PBS decisions.

Evidence from RCTs and economic evaluations is useful for making reimbursement decisions and answering questions pertaining to populations of patients, the limitations of making inferences from such evidence to individual patients have been described.(614) Heterogeneity of treatment effects between patients may reflect, for example, individual diversity in severity and manifestations of disease, and vulnerability to adverse effects. This leaves an important gap in some instances when considering the clinical situation of an individual patient. For example, the clinical situation of an individual patient, especially those who differ from the average, is not always reflected in the data submitted in support of the listing of the drug and the eventual criteria for access. Further, we are moving towards an era of 'personalised medicine' as more is learnt about disease and drug mechanisms and clinical research more skilfully dissects out responses in sub-sets of patients. At a logical as well as ethical level, it seems increasingly reasonable that patients near the margins of eligibility criteria for access to various HCMs should be considered

individually because of the uncertainty in factors contributing to success of treatment (adequate clinical improvement) in each individual.

"Accountability for reasonableness" and the Quality Use of Medicines support the position that an accessible and transparent mechanism for fair review of grievances be established as part of the PBS system. Beyond procedures to handle grievance, it is proposed that contentious cases could be dealt with ethically and formally. To some extent, pharmacists and medical advisors with clinical knowledge from Medicare Australia who assess applications for subsidised high-cost drug treatments have acted as a "review" panel but the process is informal (a finding of the interview study; Chapter 3) and not subject to public review. Martin and colleagues (63) in a study on access to medical care found that when appeals occur informally (through negotiations with individual clinicians on behalf of a patient), as occurred anecdotally with access to TNF inhibitors, the process was felt to be either non-existent or deficient. An appeal process for individual patients proposed here must have the necessary legitimacy (open, fair, and consistent) and be part of a defined mechanism when dealing with the serious health problems of individual citizens. The operational details would need to be worked out collaboratively by stakeholders in order that the appeal mechanism does reflect the ethical framework, the National Medicines Policy, and the integrity of the PBS. This present work suggests that formal mechanisms for fair grievance and to deal with appeals for individual patients who have been denied access, but where there might be reasonable grounds for approving access, could manage and reduce many of the tension that emanates from the conflict between "public good versus individual care". Even if the result of an appeal was the rejection of a request for access, justification provided to clinicians, patients and representative groups would improve understanding and more likely acceptance. There would still be limits within this

proposed system in that it would be applicable to relatively few patients; and secondly, price-volume agreements as a form of risk-sharing between sponsor and government, would remain in place to limit financial exposure of the government. Risk-sharing agreements would also maintain a 'disincentive' to stakeholders to abuse the mechanism.

In conclusion, the PBS is instituting significant changes to manage access to medicines. That decisions on drug reimbursement and access criteria should be based on the best clinical and economic evidence is agreed to and supported for efficient and equitable allocation of scarce resources. Inevitably some patients will be denied access to some medicines. This will be better accepted if the community is educated and involved in open dialogue about priorities and values, and has confidence that the system and decision-making process is legitimate and fair. This will require a continuing commitment to greater transparency by government and the pharmaceutical industry, and a willingness to consider continued improvements to the system. Clinicians and patients are more likely to endorse criteria developed through an inclusive, transparent, decision-making procedure. Thus these stakeholders' commitment to work within the system is enhanced and integration with the individual circumstances of patients for optimal clinical, economic, and ethical outcomes is more likely secured. Greater professional and political accountability in the provision of medicines will lead to responsible use of public resources, and in turn strengthen the sustainability of systems such as the PBS. An ethical analysis of the PBS processes has been overlooked as a useful mechanism for assisting in refining the PBS to meet its goals more effectively and with stronger community support. The analysis presented in this chapter and this thesis broadly suggest that a strong sense of community ownership is not only desirable but also likely to preserve and protect public systems such as the PBS against the

challenges posed by limited resources. The "accountability for reasonableness" and National Medicines Policy frameworks clearly support the contention that a formal mechanism for review of all PBS decisions at a central decision level should be incorporated in our system. In addition, a mechanism for fair grievance is an obvious need and ethically necessary. The PBS in Australia is widely acknowledged to be outstanding. These proposals are offered to address issues identified at the margins of the system in the provision of very high cost medicines. Establishment of these embellishments to the PBS system would ensure that the PBS continues as an ethically sound system.

8. DISCUSSION AND CONCLUSION

"We should not be afraid to think of new ways and ideas to improve the system and to make it more able to meet the challenges which are ahead." – Lloyd Sansom

This chapter discusses the relevance and significance of the research projects described in this thesis using primarily the framework of the National Medicines Policy and highlights areas where findings of this work suggest improvements are possible. Future directions of research on this subject are also proposed.

8.1 Discussion: The National Medicines Policy framework

Despite studies conducted describing the decision-making processes for drug reimbursement in other countries, research and data for the Australian setting at the national level are extremely limited. This is disappointing as findings from rigorous research on the Australian context would be of considerable value for other countries and health systems because: (a) Australia was the first country to establish a mandatory requirement for economic evaluation as part of submissions for listing medicines on a national formulary. Published data on the drug subsidy process of the Pharmaceutical Benefits Scheme (PBS) and decision-making process of the Pharmaceutical Benefits Advisory Committee (PBAC) would have considerable value for decision makers in other health systems; (b) evolution of the drug subsidy system is inevitable given the rapidly changing 'pharmaceutical' environment. A solid evidence base derived from comprehensive research and evaluation should be the basis to inform developments in the system (rather than purely based on logic and theory); (c) there has been very little qualitative or

quantitative data describing the PBS process and the outcomes (clinical and economic) of Australia's unique access scheme for high-cost medicines (HCMs); and (d) the paucity of quality evaluations of the outcomes of authority-required prescribing in Australia should be of concern to patients, healthcare professionals, administrators, and others since this policy is commonly used.

The series of studies reported in this thesis, using qualitative and quantitative research methods to answer different but complementary questions, form an extensive evaluation of the access arrangements for HCMs in Australia focusing on the anti-rheumatic biologicals as an example. A critical analysis of ethical issues arising from the access arrangements was also conducted as a pertinent component of this evaluation. It has been proposed that change is not brought about by only describing and evaluating the issues, but also by implementing strategies to close the identified gaps.(57) The next section highlights areas where improvements are possible, in light of Australia's National Medicines Policy (described in Chapter 2), and recommendations are proposed to strengthen the current system of access to HCMs (these are colour-highlighted in Figure 8.1).
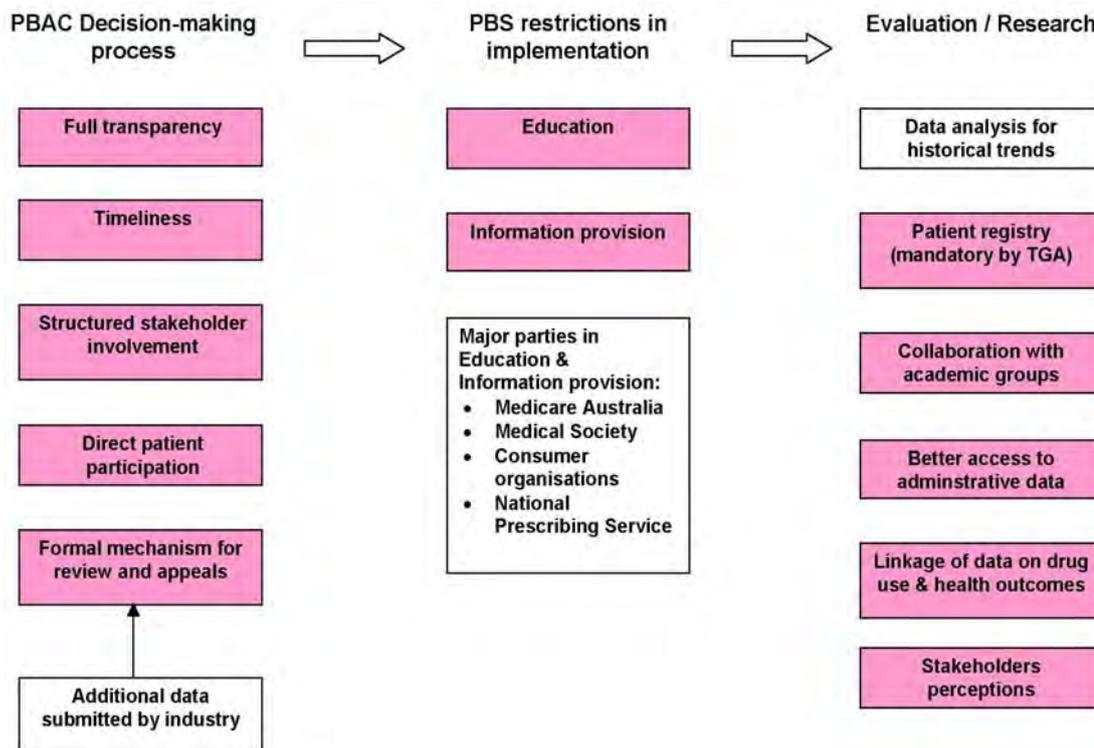
Figure 8.1 Areas for possible improvement identified in the current system of access to HCMs in accordance with the National Medicines Policy

HCMs= High cost medicines; PBAC=Pharmaceutical Benefits Advisory Committee; PBS=Pharmaceutical Benefits Scheme; TGA=Therapeutic Goods Administration

8.1.1 Partnership

Partnership between stakeholders of the pharmaceutical sector is a fundamental component of the National Medicines Policy and the national Quality Use of Medicines strategy. The "partnership" concept promotes that all groups be engaged in a cooperative manner to bring about better health and economic outcomes for all stakeholders.(238) A unique example of extensive stakeholder involvement was that which led to the PBS-listing of anti-rheumatic biologicals (described in Chapter 2). The qualitative study (Chapter 3) found that there had been increased communication and collaboration between key stakeholders (the PBAC, medical practitioners, and sponsors). There was also involvement of a wider group of stakeholders (namely, health administrators and public servants of Medicare

Australia and of the Pharmaceutical Benefits Branch of the Department of Health and Ageing); these stakeholders now routinely participate in discussions leading to decisions on PBS-listing and the details of PBS restrictions on access to HCMs. Stakeholder collaboration was crucial in arriving at a timely establishment of the 'interchangeability rule' that allows patients to trial different anti-rheumatic biologicals (Chapter 3 & Section 7.2.8), representing a further step along the path of stakeholder involvement. These developments are inherently sensible as well as accepting the challenges and opportunities offered by the National Medicines Policy framework. At a very simple level, participation in decisions by stakeholders delivers a degree of ownership, which is appropriate as the PBS is a community asset that needs community support. The groundwork has been successful and the process of gaining and modulating access criteria to high cost anti-rheumatic biologicals in a responsible way as described in this thesis is a good starting point.

There is now a good opportunity for further improvements in the domain of stakeholder involvement and ownership of decisions (Chapters 3 & 7). For example, direct participation by consumers and patients (Figure 8.1) in future processes of decision-making on subsidy and access criteria is needed to ensure that decisions are seen to be legitimate, fair, and worthy of wide community support. This approach is likely to achieve a better balance of science, social, and ethical values inherent in such decisions, not only from the consumer perspective, but also simply from a deeper understanding of the basis for decisions. What is needed now is a more formal structure for increased involvement of stakeholders (Chapter 7). Proper stakeholder involvement will require: (i) disclosure of funding sources and conflicts of interest from individual participants in the decision-making process as this is critical for a transparent, trust-based partnership, and (ii) increased ability of stakeholders who are to participate in the process to make informed contributions.

Ability of stakeholders to make informed contributions can be increased through: (a) sufficient access to unbiased, good quality information upon which each stakeholder group can form opinions (clearly the industry has an advantage in accessing information), (b) the establishment of a mechanism to ensure that the information provided to stakeholders is indeed accurate, balanced and useful, and (c) provision of training and support for stakeholders, particularly for clinicians, individual patients, carers, and the public, so that they can be appropriately informed and thereby truly involved in the decision-making processes. The Consumers Health Forum and Medicines Australia collaboratively developed a manual to guide consumer organisations in their interactions with the pharmaceutical industry.(269) Adequate access to credible information and training and support for stakeholders also is likely to reduce any unbalanced influence of the industry on stakeholder perspectives. The processes followed by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom have been described in Chapter 7. Areas in the decision-making process where the PBAC could consider whether the NICE approaches have some merit have been highlighted (Section 7.6), in particular, the provision of support and training for patients and the public, and the structured and formal stakeholder engagement processes.(602) It would be useful to examine carefully the areas for possible improvement that might arise from such a comparison despite the profound differences in the role and responsibilities of the respective Committees. Serious attention to the development of a "best model" for stakeholder involvement in the PBS-listing process, whereby all relevant stakeholders have an opportunity to participate, is urgently needed. Structured deliberations and consultation over time will also enhance the efficiency and quality of input. Furthermore, the PBAC decision-making process and stakeholder consultation once formally developed will need constant review so that high quality data gathered from such evaluations is the basis for subsequent improvement.

8.1.2 Access to high-cost medicines

The Commonwealth government and the PBS have demonstrated a commitment to ensure community access to HCMs. Patient co-payment for high-cost biologicals has remained the same as for standard prescription medicines, despite models of tiered patient cost-sharing for HCMs being suggested.(94)

The PBS has demonstrated its reliability as a "supply" system. Special considerations were made for patients who were treated with biologicals through clinical trials prior to PBS availability in order to secure their continued access. Furthermore, etanercept, adalimumab, and anakinra, administered by self-injection, were made available by the PBS under Section 85, that is, they were accessible through community pharmacies without long waiting times once an authority for prescribing had been granted, although the administrative process can be cumbersome (further discussed in Section 8.1.4). Infliximab, administered by infusion, is prescribed by specialised hospital units and dispensed through pharmacies associated with public and private hospitals that participate in the Highly Specialised Drug Program.

The experience with biologicals demonstrated that it is possible to make expensive medicines available and affordable for the community and individual patients, and this was an important accomplishment. However, a crucial recommendation for future focus arising from the present research is that there needs to be a public discussion to determine the fundamental principles and processes of targeted access to expensive medicines (Chapter 3). Genuine "partnership" is the

fundamental basis of such community discussion to ensure ownership, as described in the previous section.

The time taken to gain access to these innovative and effective biological medicines via the PBS in Australia was a concern. It took about 40 months from marketing approval by the Therapeutic Goods Administration (TGA) to achieve PBS subsidy of etanercept (the first biological) in August 2003. This period was relatively longer than for other prescription drugs according to the Productivity Commission,(216) although the average time taken for medicines to be PBS-listed once approved for marketing was not reported. Further, this PBS-listing appeared, to many rheumatologists, to be delayed given the available evidence of safety and efficacy in the literature and the wide and successful use that had occurred for a number of years overseas. Community concern about the delay in subsidised access was also expressed (Chapter 3). It must be noted, however, that as this was a first experience of extensive stakeholder consultation, not surprisingly the negotiation period was prolonged. Other critical factors that are likely to delay the time taken to PBS-listing include: the willingness (or reluctance) of the sponsor to make the process transparent and inclusive of other stakeholders (namely, clinicians and patients), submissions with major flaws or poorly validated claims for cost-effectiveness,(271) and the process of price negotiation between the PBS and the sponsor.(272) Importantly, the role of the PBAC and its sub-committees should not be understated as the time, expertise and diligence that is invested not only results in cost-effective use of PBS medicines, but also there is the potential for 'harm' (non-cost effective use) if medicines are made widely available without having been thoroughly assessed. Recently government has made efforts to streamline the PBS process to deal better with the time taken to list medicines.(272) The research undertaken in this thesis supports the contention that early, structured and effective engagement

of all relevant stakeholders that is properly established would likely deliver not only even more widely 'owned' decisions but also PBS-listings of HCMs in a timely fashion.

The example of the debate on the 'rheumatoid-factor positivity' requirement for eligibility for access in 2004 (Section 7.2.6) illustrated that there was a need for greater transparency of the rationale of PBAC decisions, as well as of the deliberations of the PBAC and of any stakeholder consultations. Without increased transparency, understanding the PBAC decisions is a serious challenge. This is because the reasons for rejecting applications or delays in PBS-listing are offered by the industry only to interested parties e.g. clinicians and consumers, and therefore, a balanced view is unlikely to be presented when PBAC is unable to defend its decisions by tabling the data upon which the decisions were based. Transparency of PBAC decisions has increased dramatically over the study period (August 2003 to August 2006), as described in Section 7.3. Greater transparency was an agreed goal of the Australia-United States Free Trade Agreement and the PBAC is to be commended for its achievements to date, in particular, publication of Public Summary Documents is a very important milestone for the PBS.(85, 268) It is important to note, however, that "commercial-in-confidence" data are still retained by the industry. Full transparency of all clinically relevant information and economic assessments (e.g. clinical trial methods, data and results) that are part of major submissions (Figure 8.1) is crucial with respect to diminishing power differences between the key stakeholders engaged in consultations and to enable genuine participation; "commercial confidentiality" should be confined to details of manufacture and formulation only. Greater accountability by key stakeholders engaged in stakeholder consultation processes is critical and will lead to better communication with their constituencies (Chapter 3). Physicians and patients are

more likely to endorse restrictions on access (including the definition of "target patient population") developed through a truly inclusive, transparent decision-making procedure.

The PBS access arrangements for high-cost anti-rheumatic biologicals have evolved over the study period (namely, removal of the requirement for 'rheumatoid-factor positivity', and the introduction of 'interchangeability rule'), reflecting review of the access arrangements such that relatively timely adjustments have been made (Chapter 7). These modifications as well as evidence of a considerable commitment towards greater transparency demonstrate that the PBAC has been accountable and committed to ameliorate problems and improve the access to HCMs. However, whether changes (or "updates") to criteria for access occur or not appears to be '*ad hoc*' to some extent, there being no formal mechanism for appeal or review of decisions by physician or patient organisations at least. A publicised formal process for review of all PBS-listing decisions and access restrictions to accommodate reasonable arguments and/or new clinical and economic evidence (Figure 8.1) is thus a crucial gap that needs to be filled (Section 7.4). The PBS would then be more truly aligned with the National Medicines Policy.

In the context of fiscal constraints, limits on therapeutic choices for individual patients are inevitable. In order to further strengthen the PBS system, this thesis identified a need to specifically incorporate ethical considerations into access to medicines via the PBS. Australia's National Medicines Policy recognises the tension between meeting the needs of both the individual and the community. However, a need for a better balance of the tension between "population benefit" and "individual care" in the context of access to HCMs has been identified and highlighted by the

current research (Chapters 3 & 7). This improved balance could be achieved by having a decision-making process that is fully transparent with structured stakeholder consultation, a perspective that is clearly supported by the ethical framework "accountability for reasonableness" that is grounded in procedural justice and emphasises democratic procedures, and by the National Medicines Policy. An ideal pharmaceutical supply and equity of access system (and it is acknowledged that the PBS is already very good and highly regarded internationally (1)), the author believes, should ensure cost-effective drug treatments while at the same time being responsive enough to explore alternative access arrangements for individual patients or specific patient groups when these are warranted. Particularly in the case of very high cost medicines (broadly, medicines whose acquisition cost is greater than A$10,000 per patient per treatment course – Section 2.4), self-funding by most patients is not a realistic option. Several approaches could be explored. Firstly, a suggestion is that arrangements could be established under the PBS to provide subsidised access to a PBS-listed medicine for a single patient in whom acceptable cost-effectiveness has not been demonstrated but there is evidence that the drug is efficacious and where PBS access criteria are largely met. Such an application for the supply of a PBS medicine would require approval from a delegate in the PBS, and this could be given on a patient-by-patient basis to reflect the needs of the individual patient. Conditions should most likely include compulsory clinical monitoring and reporting. This approach is similar to the Special Access Scheme operated by the TGA (199) that enables individual patients to apply for access to unregistered therapeutic agents. Secondly, another innovation to improve the public support for PBS decisions and access restrictions would be a formal mechanism for review of grievances and appeal of contentious cases for access to HCMs that is open, fair, and consistent, an approach that would be aligned with "accountability for reasonableness". It would be applicable to relatively few patients and price-volume

agreements as a form of risk-sharing between sponsor and government should remain in place to limit financial exposure of the government as well as maintain a 'disincentive' to stakeholders to abuse this proposed mechanism (Section 7.8). Finally, arrangements could be established under the PBS to prescribe certain medicines only within a controlled trial. This is an option proposed by Glasziou (615) to enable prescription of promising drugs for which conclusive evidence of cost-effectiveness is inadequate. This could apply to an already PBS-listed drug proposed for a new indication; the PBS might fund a portion of the trial costs if criteria including public interest and equity were met. Such an approach could also be used to prescribe a PBS-listed medicine for subgroups of patients in whom acceptable cost-effectiveness had not been demonstrated but where there are strong evidence-based grounds that cost-effectiveness was most likely if, for example, enough patients could be gathered to collect the necessary data. The proposed options would undoubtedly add to the complexity of the PBS system and the Medicare Australia administrative procedures. Clearly, collection of high quality clinical and economic data to demonstrate the cost-effectiveness of the product in actual clinical use in its various indications would be a benefit.(166) The impact on resources is difficult to predict. The cost of supporting such "special" access could be offset by the savings in other areas of the health system and reduced number of delayed listings of some medicines.(615) Price paid by government to sponsors could depend on whether projections of outcomes delivered were actually achieved and be reviewed on a regular basis. Current strategies governing "continuation" of high-cost drug therapy under the PBS could also be used to manage the "special access arrangements" proposed above. These strategies, that are already in place for access to HCMs under the PBS, are: (i) the level of 'adequate' response to treatment is discussed explicitly with patients and agreement on this issue prior to commencement of therapy is addressed, (ii) evidence of adequate benefit on some

appropriate clinical or biological test is required after an agreed, specified trial period, and (iii) written consent is obtained from patients who start taking the drug to acknowledge that subsidised treatment will only continue if the predetermined response criteria are achieved (Section 2.5). This research suggests that such additions could manage and reduce many of the tensions arising as a result of the "public good versus individual care" feature inherent in access schemes such as the PBS (Section 7.8). The main winners would be the Australian population because better value for the money spent by the PBS would be obtained and greater patient access to efficacious but expensive medicines would be enabled.

Increasing administrative requirements are a threat to the acceptance and smooth running of such access schemes, and lead to an increased use of resources. The administrative agency, Medicare Australia, has increased its efficiency in governing patients' access to HCMs over the study period. It has increased significantly the amount of information available on its web-site. Communication between Medicare Australia and the PBAC and its sub-committees has increased and become more structured (Chapter 3). These improvements should allow more efficient and better access to HCMs. Again, such processes and communication being part of the PBS system, should be subject to examination and research.

Equity of access to HCMs needs to be strengthened across the health system. It has been reported that availability of HCMs varied across public hospitals in Australia.(46, 195) Clearly some hospitals are specialised in treating particular medical areas (e.g. renal transplant) and thus selection and usage of drugs will be different at each institution. However, assuming the same clinical need, there is evidence that equity of access to HCMs across hospitals is not being achieved

currently. A qualitative study by Gallego found that decision-making regarding allocation of resources to HCMs was inconsistent between hospitals; hospitals utilised different approval mechanisms and procedures.(46) Inconsistent decision-making processes and drug budgetary control in individual hospitals contribute to inequality in access to HCMs across hospitals.(46, 195) There is a need to enhance the consistency of access to HCMs via both the PBS and hospitals to uphold the principle of equity of access so that our national health system as a whole is not undermined and citizens are dealt with fairly.

8.1.3 Quality, safety and efficacy

A system for the ongoing examination of real-world experience of medicine use and outcomes, particularly for pharmacovigilance purposes, is a national priority. While continuous monitoring of patients is required as part of the PBS access scheme for HCMs including the anti-rheumatic biologicals, this monitoring requirement was not for the purpose of pharmacovigilance. Examples from the United Kingdom and Sweden (Section 4.5) demonstrated that support from regulatory authorities is critical for a successful patient registry. Australia's TGA (as well as the PBS) has had limited collaboration to date with the Australian Rheumatology Association (or other medical societies) with respect to establishing patient registries as a basis for a proactive drug safety surveillance system. This is an important area where the access arrangements for biologicals appear to be inconsistent with the National Medicines Policy. However, a more recent example, bosentan (PBS-listed in 2004), demonstrates that efforts have been made by the PBS to ameliorate this situation where, in this example, a patient registry is part of the risk-sharing agreement between the government and the sponsoring company.

A need to enhance the post-approval safety surveillance of medicines is increasingly recognised, especially for biopharmaceuticals which often have new mechanisms of action. Etanercept was approved for licensing in Europe on the condition that a long-term follow-up scheme be established to monitor safety; national registers for biologicals have been established in most countries in Europe (Section 4.5). This scheme provides a model that Australia's TGA could follow (Figure 8.1). The TGA could thereby be a more involved partner in the area of access to HCMs and quality use of medicines generally.

In addition, collaboration between TGA and PBS would be beneficial to ensure timely access to medicines in the community. For example, once a novel, effective medicine is registered, then the TGA could notify the PBS without waiting for the sponsor to make a submission for PBS-listing. That is, the Government could assume a proactive role and an approval by the TGA could be a trigger for the PBS-listing process to begin. The first step here proposed is stakeholder involvement (Section 8.1.1) which would include the identification of the appropriate stakeholder groups and then engaging them in an organised manner to achieve a more efficient PBS-listing process. The integrity of the PBS subsidy process that evaluates all available data on a medicine rigorously before listing recommendations must be maintained. The wisdom of all stakeholders working together is more likely to deliver a system of access to medicines that is safe and effective, but also affordable and efficient.

8.1.4 Quality Use of Medicines

The PBS criteria for access to biologicals for treatment of rheumatoid arthritis (RA) were primarily evidence-based, including the requirement to trial conventional disease-modifying anti-rheumatic drugs, which was also a reasonable and practical strategy in the context of limited healthcare resources (Chapters 3 & 7). The requirement to trial conventional disease-modifying anti-rheumatic drugs has also had an unforseen but beneficial impact on the practice of rheumatology, namely re-evaluating past treatments and, in effect, inducing a more systematic and comprehensive approach to the treatment of RA nation-wide (Chapter 3).

Undoubtedly it is important that PBAC recommends drug subsidy on the basis of best available evidence of clinical and cost-effectiveness at the time of the submission, thus enabling timely introduction of new pharmaceuticals under the PBS. However, this work suggests that formal mechanisms for challenge and dispute resolution coupled with timely revision of PBS criteria for access to medicines (including HCMs) in light of further evidence and/or arguments are reforms needed in the PBS system (Figure 8.1) to strengthen access (as mentioned previously) as well as enabling quality use of medicines.

Unlike standard prescription medicines where patients can fill a prescription at a pharmacy and obtain the medicine readily, burdensome administrative requirements have the potential to impede 'timely' access to HCMs for patients. The bureaucracy of the process is a Quality Use of Medicines issue. A finding of the interview study (Chapter 3) was that even if patients have already been approved for access, ongoing extensive efforts must be made to prepare applications to Medicare Australia to gain continued access following the initial approved period of supply.

This process includes a continuous cycle of the following tasks: waiting for the 'authority prescription' from Medicare Australia to arrive in the mail for the patient, ordering pharmaceutical product from the pharmacy (usually on a monthly basis), and coordinating laboratory tests and rheumatologist consultations for the next 6-monthly assessment. The logistics of coordinating these tasks within the specified time interval required by Medicare Australia are challenging to patients and were described as "anxiety-provoking" (Chapter 3). In contrast, the increasing stakeholder involvement and communication, and greater transparency in recent years, as noted, are important for better facilitation and implementation of PBS restrictions. These significant steps forward are concordant with the Quality Use of Medicines strategy.

Better knowledge about the PBS and the principle to target access to medicines to subgroups of patients where acceptable cost-effectiveness has been demonstrated, in particular, HCMs, by health professionals and the community was identified as an issue that needs to be addressed (Chapter 3). Physicians, other health professionals, patients, and the public need to be better informed about the analyses that underpin PBAC decisions so that they understand and can, therefore, endorse the restrictions on access to medicines. Publication of Public Summary Documents about PBAC decisions on individual medicines is likely to assist prescribers to select more appropriately among many different pharmaceutical products for treating a disease, thus is concordant with the Quality Use of Medicines concept. The 'Patient Acknowledgement' process (which patients are required to sign a form acknowledging that treatment will only continue if response is satisfactory in order to gain access to HCMs) provides an important and convenient opportunity for disseminating balanced information and educating patients about the constraints on the PBS system. More education and better provision of information are likely to lead to increased public appreciation of the challenges that these

medicines pose to the PBS and would be concordant with the Quality Use of Medicines strategy and the National Medicines Policy framework. Medical societies and the National Prescribing Service are trustworthy partners in this aspect (Figure 8.1). Consumer organisations (e.g. the Arthritis Foundation) have an important role in providing patient support and in disseminating appropriate information (Chapter 3). Increased involvement and education by general practitioners, other health professionals such as pharmacists, could also benefit patients and enhance the successful development and implementation of PBS access arrangements for HCMs to the "targeted patient population".

8.1.5 Evaluation

Evaluation is a critical component of both the Quality Use of Medicines strategy and the National Medicine Policy framework. It is self-evident that careful assessment of the outcomes of the PBS and the HCM access programs be a high priority on the basis that this system is so important to the health of citizens and also requires major expenditure of public resources. Medicare Australia maintains reliable records on prescription claims and medical services claims. However, major barriers to an effective evaluation and evidence-based enhancement of access to biologicals, discussed in Chapter 4, include a lack of a formal evaluation system and political will, privacy concerns, legislative restrictions on linking data on medicine use and health outcomes, and difficulty in accessing administrative data. Further, the additional individual patient information collected as part of the controlled access to HCMs was not electronically captured by the administrative database, thus, we urgently need better information systems to collect, store, and analyse data pertinent to the efficacy, safety and cost-effectiveness of these and other expensive medicines.

In the absence of linked individual-level data on medicine use and health outcomes, population-level aggregated data were used to evaluate the impact of the PBS criteria on the use of anti-rheumatic drugs and provided useful insights on biological utilisation patterns in Australia. The utilisation and expenditure on biologicals for treating RA under the PBS over the first two years of access was found to be conservative with geographical variation in uptake across Australian States and Territories that roughly correlated with *per capita* adjusted number of rheumatologists. Reasonable rates of continuation of biological therapies in Australia (approximately 65%) suggest that the access arrangements have effectively targeted the patient sub-set identified as likely to benefit adequately enough to gain continual approval (Chapter 5). Trends in the utilisation of non-biological anti-rheumatic drugs have not changed since the availability of PBS-subsidised biologicals, based on population-level, aggregated data. The uptake of leflunomide demonstrated less variability across the States and Territories than that observed for biologicals, although the trends were similar (Chapter 6).

In addition, this research undertook evaluation of the HCM access system using qualitative methods that explored stakeholder views and experiences. The strength of this work was to use qualitative methodology to ascertain for the first time stakeholder perceptions concerning the role and functioning of the PBS, with a focus on high-cost anti-rheumatic biologicals. The premise was that these sorts of analyses have the potential to influence and even direct continued improvement, and complement quantitative evaluation (Chapter 3). The findings from qualitative investigation of the sort undertaken have increased importance in Australia because of the difficulties presently of accessing individual-level data needed to examine the health outcomes associated with the use of HCMs in proper detail, as noted previously. The investigations performed in this research suggest that qualitative

methodology and approach has much value in providing an understanding and leads to suggestions of improvements in systems like the PBS, and should remain an important element in evaluation to gain a full picture even when data-linkage and other quantitative approaches are more feasible (Figure 8.1).

Better access to comprehensive and reliable measures of the value of pharmaceutical expenditure and health gains was emphasised by this work as a key pre-requisite for effective external evaluation. Linkage studies of individual, de-identified, longitudinal prescribing, and health and demographic data sets are needed to properly understand the effect of funding HCMs on a national level. A review of historical trends of medicines and services used by patients based on individual-level data would provide the evidence-base necessary for sound evaluation post-implementation of interventions such as PBS access arrangements for biologicals. Use of all available information, that is, worldwide information from pre- and post-market trials, voluntary adverse drug reactions reporting *plus* findings from a routine system for ongoing, systematic examination of post-subsidy experience of medicine use and outcomes using linked observational data,(313) is urgently needed to serve patients, clinicians, sponsors, and regulatory authorities (Figure 8.1). In order to manage legitimate concerns about patient privacy and confidentiality, an opportunity worthy of consideration is to request the consent from patients to access their individual data around HCM provision. This could be achieved as part of the *Patient Acknowledgement For*m used in the process of accessing HCMs. This would be an important possible step towards the establishment of a proactive monitoring system.

Lessons learnt on access to HCMs under the PBS and through hospitals should be integrated in such a proactive monitoring system. Post-subsidy evaluation could be a collaborative effort between researchers, government, the pharmaceutical industry, and the other stakeholders. Government should be committed to enhancing the accessibility to data and information, taking into account privacy considerations, and to encouraging the evaluation and publication of policy-oriented studies/evaluations to enable the development and adoption of potentially more successful approaches. Government also has a role in encouraging interactions between decision makers and researchers so as to increase the relevance of the research enterprise into critical policy questions, and to assure adequate funding for studies that fill high priority gaps in knowledge in the area of pharmaceutical policy development and evaluation. Continuing evaluation and reporting of evidence from real-world population studies will advance sustainability of the PBS to support equitable access to medicines and quality use of medicines.

8.1.6 Responsible and viable pharmaceutical industry

Through the National Medicines Policy, industry is expected to communicate directly, clearly, and ethically with health professionals, and provide appropriate, non-promotional information to consumers, while the government should be committed to allow reasonable economic returns to the industry. The standards for the ethical marketing and promotion of prescription pharmaceutical products in Australia are governed by Medicines Australia's Code of Conduct.(616) The use of risk-sharing agreements between pharmaceutical sponsors and the government as a means to minimise government financial risk while supporting a viable industry has been an important feature of the access arrangements for HCMs in Australia. Usage of biologicals over the first two years of PBS-listing has been conservative, as noted.

This can be seen as concordant with the goals of the National Medicines Policy and the Quality Use of Medicines strategy as all stakeholders have an incentive to align the uptake of HCMs with agreed projections at the time of listing. From the qualitative study (Chapter 3), it was found that pharmaceutical companies were helpful in providing information and materials to clinicians. Some sponsors set up 'biologic clinics' in some hospitals to provide assistance (this is likely to be a marketing strategy). The promotional activities of the sponsors of biologicals have not been found to be discordant with the PBS prescribing criteria. The risk sharing arrangements between the Government and the sponsors support this approach because inappropriate use or leakage would lead to economic damage to the sponsor company. The prescription medicines industry organisation, Medicines Australia, recently collaborated with government in a review with the goal to improve efficiency, effectiveness and transparency of the PBS processes, as well as enhancing timely access to effective medicines.(272) Medicines Australia also collaborated with the Consumers Health Forum towards a manual to guide consumer organisations in their interactions with the pharmaceutical industry.(269) However, as described previously (Section 7.3), 'commercial-in-confidence' concerns of the pharmaceutical industry remains a sticking point and apparently precluded industry from making more detailed information included in submissions to PBS available publicly. Increased efforts by industry towards greater transparency of submissions for PBS subsidy are clearly needed. At least data of a clinical nature and significance, i.e. comparator studies, needs to be released into the public domain as it is critical information to inform optimal clinical use of the drug. In addition, the IMS data set is useful for drug utilisation studies because it contains valuable details on total wholesale pharmaceutical distribution to pharmacies, hospitals and non-retail markets (Chapter 4). Currently, the government does not access this data set despite previous interactions with the IMS Health Incorporated

having been made (personal communication, Ric Day). Efforts to achieve access to these data by the government would be a sensible approach.

8.1.7 Summary and Action agenda

In summary, the access arrangements for high-cost anti-rheumatic biologicals, as originally designed, were not entirely consistent with the National Medicines Policy. However, these arrangements have been an evolving endeavour. Throughout the study period, a number of aspects have improved and been developed, as discussed in this thesis. The direction is consistent with the National Medicines Policy framework, which is reassuring.

A number of opportunities for possible improvement have been identified in this work and these are colour-highlighted in Figure 8.1. Proposed additions to our system that would go a long way to improving the public support for PBS include: (i) a routine system for post-subsidy evaluation of medicine use and associated outcomes, (ii) formal, organised stakeholder involvement in decision-making process leading to PBS-listing and establishing arrangements for access to HCMs, (iii) full transparency regarding PBAC assessments and deliberations, and stakeholder consultations, (iv) a formal mechanism for review of and appeals against PBS-listing decisions and restrictions at a general decision level, and (v) exploration of alternative arrangements for funding an efficacious medicine for individual patients in whom acceptable cost-effectiveness has not been demonstrated but where there might be reasonable grounds for approving access. The PBS in Australia is widely acknowledged to be outstanding. These proposals are offered to address critical issues at the margins of the system in the provision of very high cost medicines that have been identified by the present work. Such

enhancements are concordant with the National Medicines Policy and are priorities that policy makers dealing with subsidised access to HCMs should focus upon. This work suggests that their adoption would enhance the sustainability of the PBS in maintaining equitable and affordable access to needed medicines with resultant improved health outcomes being delivered by this world-respected system.

8.2 Study limitations

The main methodological limitation of this work was in the domain of quantitative evaluation. This thesis included essentially an evaluation post-implementation of the access arrangements for biologicals. There was no comparison group that would allow an objective judgement of whether, and by how much, progress has been made on the various outcomes as a result of implementation of this program. Pre-post designs with comparison series to evaluate interventions would provide more valid, reliable, and actionable data on the impact of policy introduction or changes to policy.(163) Time series analysis can also provide useful information, as demonstrated by the studies that have used this approach and reported in this thesis: Chapters 5 and 6. The findings from these studies suggest that some positive outcomes have resulted from the access program (namely, controlled utilisation of biologicals from a fiscal perspective and no apparent evidence of change in DMARD prescribing). These studies also identified a wide variation in prescribing rates associated with the anti-rheumatic biologicals across Australian states and territories. This finding highlights the need for further research on factors responsible for this variability. However, it is difficult to draw concrete conclusions about the impact of this intervention on patterns of prescribing and patient outcomes nation-wide because what existed (i.e. pre-intervention individual-level baseline data on both medicine utilisation patterns and health status) before the implementation of

the access arrangements could not been ascertained in sufficient detail. Difficult access to individual-level data and current restrictions on linkage of medicine use and health outcomes data were some major obstacles as described previously. The questions as to whether the current level of utilisation represents appropriate or inappropriate prescribing of biologicals in accordance with the principles of Quality Use of Medicines, and whether this usage sufficiently or insufficiently meets the needs of RA patients cannot be addressed precisely on the basis of aggregated quantitative data and in the absence of sound epidemiological data on RA in Australia. Further, the clinical and economic outcomes of this access scheme (such as the use of healthcare services on an individual-level) cannot be addressed without examining de-identified, linked individual data over time. Notwithstanding these limitations, time series analysis does provide important insights as noted and should be used as part of the routine monitoring of the implementation of such access programs. This exercise could be conducted collaboratively between the Drug Utilisation Sub-Committee (who advises the PBAC on utilisation patterns of drugs post PBS-listing on a regular basis) and external, independent research groups.

The present research also provided in-depth qualitative data on the effects of access arrangements for biologicals and important perspectives across a range of stakeholders were gained. There are several limitations of the interview study as described in detail in Section 3.7.1. In brief, participants in this study represent individual discrete examples and do not necessarily constitute a representative sample. Inclusion of different and/or a greater range of stakeholders involved in the delivery of pharmaceuticals (for example, pharmacists, community/hospital nurses) may have elicited additional findings. Insights into some managerial perspectives were not obtained because administrators of the Highly Specialised Drug Program

of Medicare Australia who assessed patient applications for access, declined to participate in the study due to concerns about privacy. Attention to context is important; the evaluative nature of this study may have elicited more criticisms towards the access scheme for biologicals and these must be considered carefully with appropriate recognition of the strengths and improvements in the system over the study period which have also been described in this work. Further, generalising the findings to accessing other HCMs must be tentative. For example, comments about surrogate markers for the monitoring of RA cannot be directly transferred to other medical areas. Notwithstanding these limitations, a number of strategies assured a level of valid interpretation of the data and analytical generalisability. These are: (i) the major themes that arose emerged in all stakeholder groups; (ii) theoretical saturation was seemingly accomplished, and (iii) concerted efforts were made to ensure methodological rigour in this study through independent coding of data by three researchers (described in Chapter 3).

The success of a policy lies in its ability to address possible side effects that may follow. Policy evaluation studies often seem to suffer from weak research designs. Lack of rigorous evaluation was found in reviews of policy studies.(163) However, the fact that there are few rigorous studies of the impact of macro policies on drug use may stem, in part, from the complexities of the policies themselves. Despite the difficulties inherent in evaluation of policies, rigorous research designs such as quasi-experimental interrupted time-series analysis (617) and autoregressive correlation techniques should be carried out to evaluate longitudinal effects of interventions intended to contain costs, restrict prescribing and/or improve the quality of medicine use in the circumstance where individual-level, between database linkages are possible. These methods have been used extensively, notably by Soumerai and Ross-Degnan, to examine the impact of prescriber and

policy interventions on medicines use and/or health outcomes,(156-158, 479, 618) and should be employed in Australia.

8.3 Future directions

To date, limited work has been conducted regarding the use and funding of high-cost medicines (including biopharmaceuticals) via a national drug reimbursement system, such as the Pharmaceutical Benefits Scheme. There is great potential for, and value likely to accrue from, continued research in this field.

Targeting access to highly specialised drugs on the basis of an individual's genetic makeup is another innovative approach being explored by the PBS. An example is the use of gefitinib to treat non-small cell lung carcinoma in those with mutation of the epidermal growth factor receptor gene. An in-depth evaluative study using qualitative methods to explore stakeholders' views will be vitally important in order to understand the acceptability and support by the community for this individualised-medicine approach identifying patients who should have access to HCMs. The current research strongly suggests that perceptions of stakeholders, properly collected and analysed, provide valuable insights into concerns and highlight opportunities for improvement. Quantitative evaluation would provide complementary, critical evidence of the clinical and economic outcomes of this approach.

It was proposed from this work that proactive review and a mechanism to deal with appeals could manage and reduce many of the tensions between "population benefits versus individual care" in the provision of HCMs. Future qualitative studies

could explore stakeholders' views on the feasibility and development of a formal appeals mechanism as a component of access schemes for HCMs. Different approaches should be carefully examined to identify the most effective, efficient, and ethical approach for access to HCMs under drug subsidy systems to ensure they are in the best interest of all stakeholders, particularly patients.

With broadening of clinical indications for a number of biopharmaceuticals (for example, rituximab – subsidised by the PBS for the treatment of lymphoma, but recently licensed for treating rheumatoid arthritis), it is pertinent to investigate how issues such as pharmacovigilance and effectiveness in the real-world might be best undertaken for biological drugs. Also requiring investigation are: the decision-making processes regarding regulatory requirements for the approval of biopharmaceuticals for additional clinical indications, reimbursement decisions for these medicines and their multiple indications, and the access to, and use of, these drugs for each indication and the outcomes achieved, in order to identify and address potential problems. A reliable, and accurate information system is critical to these investigations.

There are limited data in the literature on the PBAC decision-making process, in particular, relating to the access arrangements for HCMs. The interview study of this evaluation of access to HCMs provided some valuable insights into the PBAC decision-making process (Chapter 3), and a critical discussion about the PBAC process and decisions using the ethical framework "accountability for reasonableness" has been presented (Chapter 7). However, how the PBAC makes decisions has not been researched in-depth. Case study methods have been used to described and examine the decision-making process in healthcare at an

institutional level, and evaluation of the process was conducted using the framework "accountability for reasonableness".(68, 69) According to Daniels and Sabin, decisions on adoption of expensive new treatments provide a window of opportunity for doing research about how resource allocation policy is actually made.(590) Investigating the PBAC decision-making process allows observation of priority setting at the national level in action. Studies using qualitative methods to closely examine the PBAC decision-making process and analyse findings in light of the ethical framework "accountability for reasonableness" are likely to identify positive and negative features and suggest opportunities for system improvement.

A desire for direct participation by patients and consumers in PBS-level decision-making processes was recognised in this research, and it was supported by the majority of study participants. The present work suggests that studies using research methods such as surveys and focus group methods, to gather information about the knowledge and views of patients across a range of medical areas and the general public about access to HCMs through the PBS would be useful. Specifically, to seek their views on the fundamental principles and processes that should apply to targeting access to expensive medicines. Findings would provide an evidence base for (i) the development of a process to better inform and involve the community in discussions about arrangements for access to medicines via the PBS, and (ii) the preparation of balanced, appropriate information to enable such discussion and consumer participation.

8.4   Conclusion

Health needs are virtually limitless. Every health care system faces some level of scarcity of resources, thus not everyone who needs a particular form of healthcare can gain access to it. Australia's Pharmaceutical Benefits Scheme has introduced significant changes to maintain the ability of Government to subsidise access to needed, effective and safe medicines at a price individuals and the community can bear in the face of rapidly escalating costs of new drugs. By examining the access scheme for anti-rheumatic biologics as an example, much has been learnt from Australia's experience. The findings of this research provide an in-depth understanding of the perceptions, concerns, and attitudes of a wide range of stakeholders about the PBS access arrangements for HCMs, specifically anti-rheumatic biologicals, and some insights into the outcomes of these access arrangements. Use of the results of this work, it is hoped, will serve to further develop the current access arrangements for HCMs, enhance the accountability of the PBS, and strengthen the quality use of medicines for the individual patient with improved health outcomes being delivered by a national public reimbursement system despite reasonable constraints on resources.

For the health of the public to be protected and improved, as well as the effectiveness and sustainability of systems for ensuring equity of access to needed medicines such as the Pharmaceutical Benefits Scheme to be maintained and enhanced, it is critical that we continuously strive to improve and expand the evidence-base for development and implementation of programs and policies that govern access to medicines. We also need to actively promote the use of the best-available, science-tested interventions that manage access to important medicines. Access to highly specialised, high-cost medicines is clearly an area that warrants

further discussion, research and review. Effective, efficient, equitable and affordable access to these important medicines via systems such as the Pharmaceutical Benefits Scheme requires this attention in order to optimise the health and economic outcomes of all stakeholders.

REFERENCES

1.   Buckley P, Marley J, Robinson J, Turnbull D, Leeder SR, Anderson WP, et al. Country profile: Australia. Lancet 1998;351:1569-1578.

2.   World Health Organisation. WHO Policy perspectives on medicines: Equitable access to essential medicines: a framework for collective action. Geneva: World Health Organisation; 2004.

3.   Miller Jr RD, Frech HE. Is there a link between pharmaceutical consumption and imporved health in OECD countries? Pharmacoeconomics 2000;18 Suppl 1:33-45.

4.   Hogerzeil H. Access to essential medicines as a human right. In: World Health Organisation: Essential Drugs Monitor Issue No. 33; 2003. p. 25-26.

5.   World Health Organisation. WHO Policy perspectives on medicines: The selection of essential medicines. Geneva: World Health Organisation; 2002.

6.   Berry LL, Seiders K, Wilder SS. Innovations in access to care: a patient-centered approach. Ann Intern Med 2003;139:568-574.

7.   Monahan J, Swartz M, Bonnie RJ. Mandated treatment in the community for people with mental disorders. Health Aff (Millwood) 2003;22:28-38.

8.   Agency for Healthcare Research and Quality. National Healthcare Disparities Report 2005. Rockville, MD: Agency for Healthcare Research and Quality, US Department of Health and Human Services; 2005.

9.   World Health Organisation. How to develop and implement a national drug policy (Second edition). Geneva, Switzerland: World Health Organisation; 2001.

10.   World Health Organisation. WHO Medicines Strategy: Progress report. Geneva, Switzerland: World Health Organisation; 2002.

11.   Quick J. Ensuring access to essential medicines in the developing countries: a framework for action. Clin Pharmacol Ther 2003;73:279-283.

12.   Quick J. Essential medicines twenty-five years on: closing the access gap. Health Policy Plan 2003;18:1-3.

13.   Correa CM. Implications of bilateral free trade agreements on access to medicines. Bull World Health Organ 2006;84:399-404.

14.   Nicol D. Balancing access to pharmaceuticals with patent rights. Monash Bioeth Rev 2003;22:50-62.

15.   Faunce T, Doran E, Henry D, Drahos P, Searles A, Pekarsky B, et al. Assessing the impact of the Australia-United States Free Trade Agreement on Australian and global medicines policy. Global Health 2005;1:15.

16.	World Health Organisation. WHO Policy perspectives on medicines: Promoting rational use of medicines: core components. Geneva: World Health Organisation; 2002.

17.	Laing RO, Hogerzeil HV, Ross-Degnan D. Ten recommendations to improve use of medicines in developing countries. Health Policy Plan 2001;16:13-20.

18.	Ratanawijitrasin S, Wondemagegnehu E. Effective drug regulation: a multi-country study. Geneva: World Health Organization 2002.

19.	AbouZahr C, Boerma T. Health information systems: the foundations of public health. Bull World Health Organ 2005;83:578-583.

20.	Richard S. The future of healthcare systems: Information technology and consumerism will transform health care worldwide. BMJ 1997;314:1495-1496.

21.	World Health Organisation. Health financing mechanisms. Available from: http://www.who.int/health_financing/issues/mechanisms/en/ (cited 12 Oct 2006). In: World Health Organisation.

22.	Organisation for Economic Co-operation and Development. OECD Health Data 2006: Statistics and Indicators for 30 Countries: Organisation for Economic Co-operation and Development; 2006.

23.	Organisation for Economic Co-operation and Development. OECD Health Data 2005: Statistics and indicators for 30 countries: Organisation for Economic Co-operation and Development; 2005.

24.	Organisation for Economic Co-operation and Development. The reform of health care systems: a review of seventeen OECD countries. Health Policy Studies, No. 5. Paris: Organisation for Economic Co-operation and Development; 1994.

25.	Gerdtham UG, Johannesson M, Gunnarsson B, Marcusson M, Henriksson F. The effect of changes in treatment patterns on drug expenditure. Pharmacoeconomics 1998;13:127-134.

26.	Gross DJ, Ratner J, Perez J, Glavin SL. International pharmaceutical spending controls: France, Germany, Sweden, and the United Kingdom. Health Care Financ Rev 1994;15:127-140.

27.	Moller Pedersen K. Pricing and reimbursement of drugs in Denmark. Eur J Health Econ 2003;4:60-65.

28.	Sitar D. Prescribing patterns for elderly community-dwelling heavy medicinal drug users in Manitoba, Canada and Jamtland, Sweden. J Clin Epidemiol 1995;48:825-831.

29.	Kildemoes HW, Christiansen T, Gyrd-Hansen D, Kristiansen IS, Andersen M. The impact of population ageing on future Danish drug expenditure. Health Policy 2006;75:298-311.

30.	National Institute for Health Care Management Foundation. Changing patterns of pharmaceutical innovation. Washington, D.C.: National Institute for Health Care Management Foundation; 2002.

31.   DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003;22:151-185.

32.   Correa CM. Ownership of knowledge--the role of patents in pharmaceutical R&D. Bull World Health Organ 2004;82:784-787.

33.   Ioannides-Demos LL, Ibrahim JE, McNeil JJ. Reference based pricing schemes: Effects on pharmaceutical expenditure, resource utilisation, and health outcomes. Pharmacoeconomics 2002;20:577-591.

34.   Okunade AA, Suraratdecha C. The pervasiveness of pharmaceutical expenditure inertia in the OECD countries. Soc Sci Med 2006;63:225-238.

35.   Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. Promotion of prescription drugs to consumers. N Eng J Med 2002;346:498-505.

36.   Hansen RA, Shaheen NJ, Shchommer JC. Factors influencing the shift of patients from one proton pump inhibitor to another: the effect of direct-to-consumer advertising. Clin Ther 2005;27:1478-1487.

37.   Moynihan R, Heath I, Henry D. Selling sickness: the pharmaceutical industry and disease mongering. BMJ 2002;324:886-891.

38.   Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 5th ed. New York: Oxford University Press; 2001.

39.   Emanuel EJ. Justice and managed care. Four principles for the just allocation of health care resources. Hastings Center Report 2000;30:8-16.

40.   Carroll JS, Johnson EJ. Decision Research. A Field Guide. Newbury Park: Sage Publications; 1990.

41.   Beattie J, Barlas S. Predicting perceived differences in tradeoff difficulty. In: Conflicts and Tradeoff in Decision Making. Cambridge: Cambridge University Press; 2001.

42.   Weber E, Baron J, Graham L. Conflicts and Trade-offs in Decision Making. Cambridge: Cambridge University Press; 2001.

43.   Hunter DJ. Desperately seeking solutions: rationing dilemmas in health care. Aust Health Rev 1993;16:130-147.

44.   Edgar A, Salek S, Darren S, Cohen D. The Ethical QALY. Ethical Issues in Healthcare Resource Allocations. Haslemere: Euromed Communications; 1998.

45.   Singer PA. Recent advances: Medical ethics. BMJ 2000;321:282-285.

46.   Gallego G. Access to high cost medicines in Australian hospitals [PhD]. Sydney: University of Sydney; 2006.

47.   Gibson JL, Martin DK, Singer PA. Setting priorities in health care organizations: criteria, processes, and parameters of success. BMC Health Serv Res 2004;4:25.

48.   Ham C. Priority setting in health care: learning from international experience. Health Policy 1997;42:49-66.

49.   Emanuel EJ, Emanuel LL. What is accountability in health care? Ann Intern Med 1996;124:229-239.

50.   Klein R. Rationing in Action: Dimensions of Rationing: Who Should Do What? BMJ 1993;307:309-311.

51.   Hoedemaekers R, Dekkers W. Key concepts in health care priority setting. Health Care Anal 2003;11:309-323.

52.   Ham C, Coulter A. Explicit and implicit rationing: taking responsibility and avoiding blame for health care choices. J Health Serv Res Policy 2001;6:163-169.

53.   Holm S. The second phase of priority setting: Goodbye to the simple solutions: the second phase of priority setting in health care. BMJ 1998;317:1000-1002.

54.   Holm S. Developments in The Nordic Countries - Goodbye to Simple Solutions. In: Coulter A, Ham C, editors. The Global Challenge of Health Care Rationing. Buckingham - Philadelphia: Open University Press; 2000.

55.   Ham C, Coulter A. International Experience of rationing (or priority setting). In: Coulter A, Ham C, editors. The Global Challenge of Health Care Rationing. Buckingham - Philadelphia: Open University Press; 2000. p. 1-12.

56.   Daniels N, Sabin J. Limits to health care: fair procedures, democratic deliberation, and the legitimacy problem for insurers. Philosophy and public affairs 1997;26:303-350.

57.   Martin D, Singer P. A strategy to improve priority setting in health care institutions. Health Care Analysis 2003;11:59-68.

58.   Al MJ, Feenstra T, Brouwer WB. Decision makers' views on health care objectives and budget constraints: results from a pilot study. Health Policy 2004;70:33-48.

59.   Mannebach MA, Ascione FJ, Gaither CA, Bagozzi RP, Cohen IA, Ryan ML. Activities, functions, and structure of pharmacy and therapeutics committees in large teaching hospitals. Am J Health-Syst Pharm 1999;56:622-628.

60.   Hasle-Pham E, Arnould B, Spath HM, Follet A, Duru G, Marquis P. Role of clinical, patient-reported outcome and medico-economic studies in the public hospital drug formulary decision-making process: results of a European survey. Health Policy 2005;71:205-212.

61.   Weekes LM, Brooks C. Drug and Therapeutics Committees in Australia: expected and actual performance. Br J Clin Pharmacol 1996;42:551-557.

62.   Daniels N, Teagarden JR, Sabin JE. An ethical template for pharmacy benefits. Health Aff (Millwood) 2003;22:125-137.

63.	Martin DK, Singer PA, Bernstein M. Access to intensive care unit beds for neurosurgery patients: a qualitative case study. J Neurol Neurosurg Psychiatry 2003;74:1299-1303.

64.	Martin D, Shulman K, Santiago-Sorrell P, Singer P. Priority-setting and hospital strategic planning: a qualitative case study. Crit Care Med 2003;31:197-201.

65.	Martin D, Shulman K, Santiago-Sorrell P, Singer P. Priority-setting and hospital strategic planning: a qualitative case study. J Health Serv Res Policy 2003;8:197-201.

66.	Martin DK, Hollenberg D, MacRae S, Madden S, Singer P. Priority setting in a hospital drug formulary: a qualitative case study and evaluation. Health Policy 2003;66:295-303.

67.	Martin DK, Giacomini M, Singer PA. Fairness, accountability for reasonableness, and the views of priority setting decision-makers. Health Policy 2002;61:279-290.

68.	Martin DK, Pater JL, Singer PA. Priority-setting decisions for new cancer drugs: A qualitative case study. Lancet 2001;358:1676-1681.

69.	Singer PA, Martin DK, Giacomini M, Purdy L. Priority setting for new technologies in medicine: qualitative case study. BMJ 2000;321:1316-1318.

70.	Ess SM, Schneeweiss S, Szucs TD. European healthcare policies for controlling drug expenditure. Pharmacoeconomics 2003;21:89-103.

71.	Australian Government Productivity Commission. International pharmaceutical price differences: research report. Canberra: Australian Government, Productivity Commission; 2001.

72.	Freemantle N, Hill S. Evaluating pharmaceuticals for health policy and reimbursement. 1st ed. Thousand Oaks, CA: Blackwell Publishing; 2004.

73.	Dickson M, Redwood H. Pharmaceutical reference prices: how do they work in practice? Pharmacoeconomics 1998;14:471-479.

74.	Bloor K, Maynard A, Freemantle N. Lessons from international experience in controlling pharmaceutical expenditure. III: Regulating industry. BMJ 1996;313:33-35.

75.	Giuliani G, Selke G, Garattini L. The German experience in reference pricing. Health Policy 1998;44:73-85.

76.	Rigter H. Recent public policies in The Netherlands to control pharmaceutical pricing and reimbursement. Pharmacoeconomics 1994;6 Suppl 1:15-21.

77.	Schneeweiss S, Schoffski O, Selke GW. What is Germany's experience on reference based drug pricing and the etiology of adverse health outcomes or substitution? Health Policy 1998;44:253-260.

78.	Drummond M, Jonsson B, Rutten F. The role of economic evaluation in the pricing and reimbursement of medicines. Health Policy 1997;40:199-215.

79.   von der Schulenburg JM. Management of cost and utilization of pharmaceuticals in Germany. Health Policy 1997;41:s45-53.

80.   Schneeweiss S, Walker A, Glynn R. Outcomes of reference pricing for angiotensin-converting-enzyme inhibitors. N Eng J Med 2002;346:822-829.

81.   Australian Government Department of Health and Ageing. Pharmaceutical Benefits Pricing Authority Policies, Procedures and Methods. Available from: http://www.health.gov.au/ (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

82.   Narine L, Senathirajah M, Smith T. Evaluating reference-based pricing: initial findings and prospects. CMAJ 1999;161:286-288.

83.   Australian Government Department of Industry Tourism and Resources. Pharmaceuticals Industry Investment Program. Available from: http://www.industry.gov.au/content/sitemap.cfm?objectID=48A506B0-20E0-68D8-ED81D261FE559437 (cited 02 May 2007). In: Australian Government Department of Industry Tourism and Resources.

84.   McManus P, Birkett DJ, Dudley J, Stevens A. Impact of the Minimum Pricing Policy and introduction of brand (generic) substitution into the Pharmaceutical Benefits Scheme in Australia. Pharmacoepidemiol Drug Saf 2001;10:295-300.

85.   Sansom L. The subsidy of pharmaceuticals in Australia: processes and challenges. Aust Health Rev 2004;28:194-205.

86.   Lofgren H. Generic drugs: international trends and policy developments in Australia. Aust Health Rev 2004;27:39-48.

87.   Martikainen J, Kivi I, Linnosmaa I. European prices of newly launched reimbursable pharmaceuticals--a pilot study. Health Policy 2005;74:235-246.

88.   Australian Government Department of Health and Ageing. Pharmacy and Government Arrangements - Fourth Community Pharmacy Agreement. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pharmacy-4cpa (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

89.   Burstall ML. The management of the cost and utilisation of pharmaceuticals in the United Kingdom. Health Policy 1997;41:71-89.

90.   Maynard A, Bloor K. Regulating the pharmaceutical industry. BMJ 1997;315:200-201.

91.   Bloom N, Van Reenen J. Regulating drug prices: where do we go from here? Fiscal Studies 1998;19:347-374.

92.   Mossialos E, Oliver A. An overview of pharmaceutical policy in four countries: France, Germany, the Netherlands and the United Kingdom. Int J Health Plann Mgmt 2005;20:291-306.

93.   Paris V. Pharmaceutical regulation in France 1980-2003. Int J Health Plann Mgmt 2005;20:307-328.

94.   Brown L, Walker A, Waters AM, Harding A, Thurecht L. Funding of high cost biotechnology and other innovative targeted therapies under the Pharmaceutical Benefits Scheme. Position Paper. Canberra: NATSEM; 2002.

95.   Fattore G, Jommi C. The new pharmaceutical policy in Italy. Health Policy 1998;46:21-41.

96.   Cranovsky R, Schilling J, Faisst K, Koch P, Gutzwiller F, Brunner HH. Health technology assessment in Switzerland. Int J Technol Assess Health Care 2000;16:576-590.

97.   Braae R, McNee W, Moore D. Managing pharmaceutical expenditure while increasing access. The Pharmaceutical Management Agency (PHARMAC) experience. Pharmacoeconomics 1999;16:649-660.

98.   Maclure M, Potashnik TM. What is direct evidence-based policy-making: experience from the drug benefits program for seniors in British Columbia. Can J Aging 1997;16 Suppl:132-146.

99.   Dickson M. The pricing of pharmaceuticals: an international comparison. Clin Ther 1992;14:604-610.

100.   Anis AH, Rahman T, Schechter MT. Using pharmacoeconomic analysis to make drug insurance coverage decisions. Pharmacoeconomics 1998;13:119-126.

101.   Anis AH. Pharmaceutical policies in Canada: another example of federal-provincial discord. CMAJ 2000;162:523-526.

102.   Huskamp H, Esptein A, Blumenthal D. The impact of a national prescription drug formulary on prices, market share, and spending: lessons for Medicare? Health Aff (Millwood) 2003;22:149-158.

103.   Motheral BR, Henderson R. The effect of a closed formulary on prescription drug use and costs. Inquiry 1999;36:481-491.

104.   Soumerai S. Benefits and risks of increasing restrictions on access to costly drugs in Medicaid. Health Aff (Millwood) 2004;23:135-146.

105.   Soumerai SB, Ross-Degnan D, Gortmaker S, Avorn J. Withdrawing payment for nonscientific drug therapy. Intended and unexpected effects of a large-scale natural experiment. JAMA 1990;263:831-839.

106.   Henry D. Economic analysis as an aid to subsidisation decisions: the development of Australian guidelines for pharmaceuticals. Pharmacoeconomics 1992;1:54-67.

107.   Johannesson M. Economic evaluation of drugs and its potential uses in policy making. Pharmacoeconomics 1995;8:190-198.

108.   Gafni A, Birch S. NICE methodological guidelines and decision making in the National health service in England and Wales. Pharmacoeconomics 2003;21:149-157.

109.   Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices - Modeling Studies. Value in Health 2003;6:9-17.

110.   Ubel PA, DeKay ML, Baron J, Asch DA. Cost-effectiveness analysis in a setting of budget constraints--is it equitable? N Eng J Med 1996;334:1174-1177.

111.   Bradley C. Uncomfortable prescribing decisions: a critical incident study. BMJ 1992;304:294-296.

112.   Wensing M, Grol R. Single and combined strategies for implementing changes in primary care: a literature review. Int J Qual Health Care 1994;6:115-132.

113.   Oxman AD, Thomson MA, Davis DA, Haynes RB. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. CMAJ 1995;153:1423-1431.

114.   Sansom L. The Australian National Medicinal Drug Policy. J Quality Clinical Practice 1999;19:31-35.

115.   Mant A. Quality use of medicines: ten years down the track. Aust Prescr 2001;24:106-107.

116.   Australian Government Department of Health and Ageing. The National Strategy for Quality Use of Medicines - Executive Summary. Canberra: Australian Government Department of Health and Ageing; 2002.

117.   Smith AJ, McGettigan P. Quality use of medicines in the community: the Australian experience. Br J Clin Pharmacol 2000;50:515-519.

118.   Roughead EE, Monteith GR, Harvey KJ, Tett SE. Evaluating Australia's National Medicines Policy using geographical mapping. Intern Med J 2002;32:66-71.

119.   Weekes LM, Mackson JM, Fitzgerald M, Phillips SR. National Prescribing Service: creating an implementation arm for national medicines policy. Br J Clin Pharmacol 2005;59:112-116.

120.   Bloor K, Freemantle N. Lessons from international experience in controlling pharmaceutical expenditure. II: Influencing doctors. BMJ 1996;312:1525-1527.

121.   Soumerai SB, Ross-Degnan D. Prescribing budgets: economic, clinical and ethical perspectives. Aust Prescr 1997;20:28-29.

122.   Schoffski O. Consequences of implementing a drug budget for office-based physicians in Germany. Pharmacoeconomics 1996;10 Suppl 2:37-47.

123.   Schreyogg J, Busse R. Physician Drug Budgets in Germany and Effects on Prescription Behaviour. J Pharmaceut Finance Econ Pol 2005;14:77-95.

124.   Busse R, Schreyogg J, Henke KD. Regulation of pharmaceutical markets in Germany: improving efficiency and controlling expenditures? Int J Health Plann Mgmt 2005;20:329-349.

125. Harris CM, Scrivener G. Fundholders' prescribing costs: the first five years. BMJ 1996;313:1531-1534.

126. Mossialos E, Walley T, Rudisill C. Provider incentives and prescribing behavior in Europe. Expert Review of Pharmacoeconomics and Outcomes Research 2005;5:81-93.

127. Wathen B, Dean T. An evaluation of the impact of NICE guidance on GP prescribing. Br J Gen Pract 2004;54:103-107.

128. Sheldon TA, Cullum N, Dawson D, Lankshear A, Lowson K, Watt I, et al. What's the evidence that NICE guidance has been implemented: Results from a national evaluation using time series analysis, audit of patients' notes, and interviews. BMJ 2004;329:999-1003.

129. Beilby J, Wutzke SE, Bowman J, Mackson JM, Weekes LM. Evaluation of a national quality use of medicines service in Australia: an evolving model. J Eval Clin Pract 2006;12:202-217.

130. Majeed A, Evans N, Head P. What can PACT tell us about prescribing in general practice? BMJ 1997;315:1515-1519.

131. Australian Government Department of Veterans' Affairs. Veterans' Medicines Advice and Therapeutics Education Services. Available from: http://www.dva.gov.au/health/veteransmates/index.htm (cited 12 Oct 2006). In: Australian Government Department of Veterans' Affairs.

132. Hillen J, Roughead E, Gilbert A, Rowett D, Azam R, Rossi S, et al. Data-driven patient-specific prescriber feedback; the Veterans' MATES project. In: National Medicines Symposium; 2006; Canberra, Australia; 2006.

133. MacKinnon NJ, Kumar R. Prior authorization programs: a critical review of the literature. J Mang Care Pharm 2001;7:297-302.

134. Birkett DJ, Mitchell AS, McManus P. A cost-effectiveness approach to drug subsidy and pricing in Australia. Health Aff (Millwood) 2001;20:104-114.

135. Hamel MB, Epstein AM. Prior-authorization programs for controlling drug spending. N Eng J Med 2004;351:2156-2158.

136. Delate T, Mager DE, Sheth J, Motheral BR. Clinical and financial outcomes associated with proton pump inhibitor prior-authorization program in a Medicaid Population. Am J Manag Care 2005;11:29-36.

137. Liaw ST, Pearce C, Chondros P, McGrath B, Piggford L, Jones K. Doctors' perceptions and attitudes to prescribing within the Authority Prescribing System. Med J Aust 2003;178:203-206.

138. Australian Government Medicare Australia. PBS authorities website. Available from: http://www.medicareaustralia.gov.au/providers/online_initiatives/pbs_authorities_online.htm (cited 12 Oct 2006). In: Australian Government Medicare Australia.

139.	Freemantle N, Bloor K. Lessons from international experience in controlling pharmaceutical expenditure. I: Influencing patients. BMJ 1996;312:1469-1471.

140.	Motheral B, Fairman KA. Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. Med Care 2001;39:1293-1304.

141.	Harris BL, Stergachis A, Ried LD. The effect of drug co-payments on utilization and cost of pharmaceuticals in a health maintenance organization. Med Care 1990;28:901-917.

142.	Motheral BR, Henderson R. The effect of a copay increase on pharmaceutical utilization, expenditures, and treatment continuation. Am J Manag Care 1999;5:1383-1394.

143.	Huskamp HA, Deverka PA, Epstein AM, Epstein RS, McGuigan KA, Frank RG. The effect of incentive-based formularies on prescription-drug utilization and spending. N Eng J Med 2003;349:2224-2232.

144.	Goldman DP, Joyce GF, Escarce JJ, Pace JE, Solomon MD, Laouri M, et al. Pharmacy benefits and the use of drugs by the chronically ill. JAMA 2004;291:2344-2350.

145.	Ganther-Urmie JM, Nair KV, Valuck R, McCollum M, Lewis SJ, Turpin RS. Consumer attitudes and factors related to prescription switching decisions in multitier copayment drug benefit plans. Am J Manag Care 2004;10:201-208.

146.	Ryan M, Birch S. Charging for health care: evidence on the utilisation of NHS prescribed drugs. Soc Sci Med 1991;33:681-687.

147.	Tamblyn R, Laprise R, Hanley JA, Abrahamowicz M, Scott S, Mayo N, et al. Adverse events associated with prescription drug cost-sharing among poor and elderly persons. JAMA 2001;285:421-429.

148.	Gibson TB, McLaughlin CG, Smith DG. Cost-sharing for prescription drugs. JAMA 2001;285:2328-2329.

149.	Schafheutle EI, Hassell K, Noyce PR, Weiss MC. Access to medicines: cost as an influence on the views and behaviour of patients. Health Soc Care Community 2002;10:187-195.

150.	Lexchin J, Grootendorst P. Effects of prescription drug user fees on drug and health services use and on health status in vulnerable populations: a systematic review of the evidence. Int J Health Serv 2004;34:101-122.

151.	McManus P, Donnelly N, Henry D, Hall W, Primrose J, Lindner J. Prescription drug utilization following patient co-payment changes in Australia. Pharmacoepidemiol Drug Saf 1996;5:385-392.

152.	Blendon RJ, Schoen C, DesRoches CM, Osborn R, Scoles KL, Zapert K. Inequities in health care: a five-country survey. Health Aff (Millwood) 2002;21:182-191.

153.	Doran E, Robertson J, Rolfe I, Henry D. Patient co-payments and use of prescription medicines. Aust N Z J Public Health 2004;28:62-67.

154. Doran E, Henry DA. The PBS community awareness campaign: how helpful is blaming patients? Med J Aust 2003;179:544-545.

155. Doran E, Robertson J, Henry D. Moral hazard and prescription medicine use in Australia--the patient perspective. Soc Sci Med 2005;60:1437-1443.

156. Soumerai SB, McLaughlin TJ, Ross-Degnan D, Casteris CS, Bollini P. Effects of Limiting Medicaid Drug-Reimbursement Benefits on the Use of Psychotropic Agents and Acute Mental Health Services by Patients with Schizophrenia. N Eng J Med 1994;331:650-655.

157. Soumerai SB, Ross-Degnan D, Avorn J, McLaughlin T, Choodnovskiy I. Effects of Medicaid drug-payment limits on admission to hospitals and nursing homes. N Eng J Med 1991;325:1072-1077.

158. Soumerai S, Avorn J, Ross-Degnan D. Payment restrictions for prescriptions drugs under Medicaid. N Eng J Med 1987;317:550-556.

159. Tseng CW, Brook RH, Keeler E, Steers WN, Mangione CM. Cost-lowering strategies used by medicare beneficiaries who exceed drug benefit caps and have a gap in drug coverage. JAMA 2004;292:952-960.

160. Hsu J, Price M, Huang J, Brand R, Fung V, Hui R, et al. Unintended consequences of caps on Medicare drug benefits. N Eng J Med 2006;354:2349-2359.

161. Burton SL, Randel L, Titlow K, Emanuel EJ. The ethics of pharmaceutical benefit management. Health Aff (Millwood) 2001;20:150-163.

162. Soumerai SB, Ross-Degnan D, Fortess EE, Abelson J. A critical analysis of studies of state drug reimbursement policies: research in need of discipline. Milbank Q 1993;71:217-252.

163. Ratanawijitrasin S, Soumerai SB, Weerasuriya K. Do national medicinal drug policies and essential drug programs improve drug use?: a review of experiences in developing countries. Soc Sci Med 2001;53:831-844.

164. Walsh G. Biopharmaceuticals: recent approvals and likely directions. Trends Biotechnol 2005;23:553-558.

165. Weinberg WC, Frazier-Jessen MR, Wu WJ, Weir A, Hartsough M, Keegan P, et al. Development and regulation of monoclonal antibody products: challenges and opportunities. Cancer Metastasis Rev 2005;24:569-584.

166. Mason J, Drummond M. Biotechnology: a special case for health technology assessment? Health Policy 1997;41:73-81.

167. Mason J. Challenges to the economic evaluation of new biotechnological interventions in healthcare. Pharmacoeconomics 1999;16:119-125.

168. van Rijkom J, Leufkens H, Crommelin D, Rutten F, Broekmans A. Assessment of biotechnology drugs: what are the issues? Health Policy 1999;47:255-274.

169.   Annemans L, Geneste B, Jolain B. Early modelling for assessing health and economic outcomes of drug therapy. Value in Health 2000;3:427-434.

170.   Drummond M, Sculpher M. Better analysis for better decisions: has pharmacoeconomics come of age? Pharmacoeconomics 2006;24:107-108.

171.   Psaty BM, Burke SP. Protecting the Health of the Public -- Institute of Medicine Recommendations on Drug Safety. N Eng J Med 2006;355:1753-1756.

172.   Wood AJJ. A Proposal for Radical Changes in the Drug-Approval Process. N Eng J Med 2006;355:618-623.

173.   Freemantle N, Blonde L, Bolinder B, Gerber RA, Hobbs FD, Martinez L, et al. Real-world trials to answer real-world questions. Pharmacoeconomics 2005;23:747-754.

174.   Willcutts D. Specialty pharmaceuticals: developing a management plan. Manag Care Q 2002;10:24-29.

175.   Rosenau PV. Reflections on the cost consequences of the new gene technology for health policy. Int J Technol Assess Health Care 1994;10:546-561.

176.   National Institute for Health and Clinical Excellence. Guidance on the use of beta interferon and glatiramer acetate for the treatment of multiple sclerosis. Technology Appraisal Guidance No. 32. London: National Institute for Health and Clinical Excellence; 2002.

177.   Department of Health (United Kingdom). 'Payment by results' breakthrough ends years of uncertainty for MS patients. Available from: http://www.dh.gov.uk/ (cited 12 Oct 2006). In: Department of Health (United Kingdom); 2002.

178.   Sudlow CLM, Counsell CE. Problems with UK government's risk sharing scheme for assessing drugs for multiple sclerosis. BMJ 2003;326:388-392.

179.   Chadwick D, Gray R. Shared scheme for assessing drugs for multiple sclerosis: dealing with uncertainties about cost effectiveness of treatments is difficult problem. BMJ 2003;326:1212-1213.

180.   Powe NR, Eggers PW, Johnson CB. Early adoption of cyclosporine and recombinant human erythropoietin: clinical, economic, and policy issues with emergence of high-cost drugs. Am J Kidney Dis 1994;24:33-41.

181.   Commonwealth Department of Health and Aged Care. The Australian Health Care System, An Outline. Canberra, ACT: Commonwealth Department of Health and Aged Care, Publications Unit; 2000.

182.   Vaughan G. The Australian drug regulatory system. Aust Prescr 1995;18:69-71.

183.   Australian Government Department of Health and Ageing. Therapeutic Goods Administration. Available from: http://www.tga.gov.au. In: Australian Government Department of Health and Ageing.

184.   Harvey KJ, Murray MM. Medicinal drug policy. In: H. G, editor. The politics of health: Churchill Livingstone: Melbourne; 1995.

185.   Graham D. The Australian Pharmaceutical Scheme. Aust Prescr 1995:42-44.

186.   Hill S, Henry D, Pekarsky B, Mitchell A. Economic evaluation of pharmaceuticals: what are reasonable standards for clinical evidence - the Australian experience. British Journal of Pharmacology 1997;44:421-425.

187.   Australian Government Department of Health and Ageing. 2002 Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee including major submissions involving economic analyses. Canberra: Australian Government Department of Health and Ageing; 2002.

188.   Australian Government Department of Health and Ageing. PBS statistics. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-stats.htm-copy3 (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

189.   Australian Government Department of Health and Ageing. Pharmaceutical Benefits Scheme - Expenditure and Prescriptions. Available from: http://www.health.gov.au/ (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

190.   Australian Government Department of Health and Ageing. Schedule of Pharmaceutical Benefits - Section 100 Arrangements. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/content/pbs-schedule-sec100 (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

191.   Australian Government Department of Health and Ageing. The Highly Specialised Drug Program. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/1CF96D8028AE509ECA2570BA001AC076/$File/bookp40_41.pdf (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

192.   Australian Government Department of Health and Ageing. Aboriginal Health Services and the Pharmaceutical Benefits Scheme (PBS). Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-indigenous (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

193.   Hall J. Incremental change in the Australian health care system. Health Aff (Millwood) 1999;18:95-110.

194.   Australian Institute of Health and Welfare. Australian's health 2004, Cat. No. AUS 44. Canberra: Australian Institute of Health and Welfare; 2004.

195.   The Society of Hospital Pharmacists of Australia. Moving forward - The funding of medicines in Australia's hospitals. Melbourne: The Society of Hospital Pharmacists of Australia (SHPA); 2004.

196.   Australian Institute of Health and Welfare. Australian hospital statistics 2002-2003. AIHW cat. no. HSE 32. Canberra: Australian Institute of Health and Welfare (Health Services Series no.22); 2004.

197.   Australian Government Department of Health and Ageing. Australian Health Care Agreements. Available from: http://www.health.gov.au/internet/wcms/Publishing.nsf/Content/Australian+Health+Care+Agreements-1 (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing; 2004.

198.   Australian Government Department of Health and Ageing. Other supply arrangements outside the Pharmaceutical Benefits Scheme (PBS). Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-supply-othersupply (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

199.   Australian Government Department of Health and Ageing. Therapeutic Goods Administration: Special access scheme at a glance - Access to unapproved therapeutic goods. Available from: http://www.tga.gov.au/unapp/sasglance.htm (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

200.   Australian Government Department of Health and Ageing. Therapeutic Goods Administration: Clinical trials in Australia - Access to unapproved therapeutic goods. Available from: http://www.tga.gov.au/docs/html/clintrials.htm (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

201.   Australian Institute of Health and Welfare. Health expenditure Australia 2001-02. AIHW Cat. No. HWE 24. Canberra: Australian Institute of Health and Welfare; 2003.

202.   Taylor RS, Drummond MF, Salkeld G, Sullivan SD. Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. BMJ 2004;329:972-975.

203.   Taylor RS, Drummond MF, Salked G, Sullivan SD. Development of fourth hurdle policies around the world. In: Freemantle N, Hill S, editors. Evaluating Pharmaceuticals for Health Policy and Reimbursement. London: BMJ; 2004. p. 67-87.

204.   Lopert R, Henry D. The Pharmaceutical Benefits Scheme: economic evaluation works .... but is not a panacea. Aust Prescr 2002;25:126-127.

205.   Australian Institute of Health and Welfare. Health expenditure Australia 2004-05. AIHW Cat. No. HWE 35. Canberra: Australian Institute of Health and Welfare; 2006.

206.   Australian Institute of Health and Welfare. Health expenditure Australia 2003-04. AIHW Cat. No. HWE 32. Canberra: Australian Institute of Health and Welfare; 2005.

207.   Kerr SJ, Mant A, Horn FE, McGeechan K, Sayer GP. Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners. Med J Aust 2003;179:403-407.

208.   Dowden JS. Coax, COX and cola. Med J Aust 2003;179:397-398.

209.   Rickard M. The Pharmaceutical Benefits Scheme: Options for Cost Control. Current Issues Brief No.12: Department of the Parliamentary Library; 2002.

210.   Viney R. Funding arrangements for pharmaceuticals: can economic evaluation promote efficiency? Aust Health Rev 2001;24:21-24.

211.   Mucklow JC. How can we afford costly medicines? J R Coll Phys Lond 2000;34:124-127.

212.   Poirier T, Gianetti V. Clinical and ethical principles on rationing high-cost drugs. Ann Pharmacother 1995;29:78-81.

213.   Crump BJ, Panton R, Drummond MF, Marchment M, Hawkes RA. Transferring the costs of expensive treatments from secondary to primary care. BMJ 1995;310:509-512.

214.   Kleinke JD. Access versus excess: value-based cost sharing for prescription drugs. Health Aff (Millwood) 2004;23:34-47.

215.   Willcutts D. Developing a management plan. Manag Care Q 2003;11:7-10.

216.   Australian Government Productivity Commission. Impacts of Advances in Medical Technology in Australia, Research report. Melbourne: Australian Government Productivity Commission; 2005.

217.   High Cost Drugs Working Party. Drug and Therapeutics Committee Template for Formulary Submissions - Decision algorithm. Available from: http://www.ciap.health.nsw.gov.au/nswtag/high_cost_drugs-wp.html (cited 12 Oct 2006). In: NSW Therapeutic Advisory Group; 2006.

218.   Australian Government Department of Health and Ageing. Pharmaceutical Benefits Scheme - Outcomes of Pharmaceutical Benefits Advisory Committee meetings. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-outcomes_full.htm (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

219.   Lu CY, Williams KM, Day RO, March LM, Sansom L, Bertouch J. Access to high cost drugs in Australia: *Risk sharing scheme may set a new paradigm*. BMJ 2004:415-416.

220.   Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 2002;46:625-631.

221.   van der Horst-Bruinsma IE, Speyer I, Visser H, Breedveld FC, Hazes JM. Diagnosis and course of early-onset arthritis: results of a special early arthritis clinic compared to routine patient care. Br J Rheumatol 1998;37:1084-1088.

222.   Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol 1989;16:585-591.

223.   Wolfe F, Hawley DJ. The long-term outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients. J Rheumatol 1998;25:2108-2117.

224.   Hawley DJ, Wolfe F. Anxiety and depression in patients with rheumatoid arthritis: a prospective study of 400 patients. J Rheumatol 1988;15:932-941.

225.   Soderlin MK, Hakala M, Nieminen P. Anxiety and depression in a community-based rheumatoid arthritis population. Scand J Rheumatol 2000;29:177-183.

226.   Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics 2004;22:s1-s12.

227.   Allaire SH, Prashker MJ, Meenan RF. The costs of rheumatoid arthritis. Pharmacoeconomics 1994;6:513-522.

228.   American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum 2002;46:328-346.

229.   Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. Ann Intern Med 1999;130:478-486.

230.   Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-1939.

231.   Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:614-624.

232.   Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.

233.   Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275-2285.

234.   van Vollenhoven RF. Switching between biological agents. Clin Exp Rheumatol 2004;22:S115-S121.

235.   Berwick DM. Continuous improvement as an ideal in health care. N Eng J Med 1989;320:53-56.

236.   Donabedian A. The quality of care. How can it be assessed? JAMA 1988;260:1743-1748.

237.   World Health Organisation. Guidelines for Developing National Drug Policies. Geneva: World Health Organisation; 1988.

238.   Australian Government Department of Health and Ageing. National Medicines Policy. Canberra: Australian Government Department of Health and Ageing; 2000.

239.   Australian Government Department of Industry Tourism and Resources. Pharmaceuticals Partnerships Program (P3). Available from: http://www.industry.gov.au/content/sitemap.cfm?objectid=48A509F9-20E0-68D8-EDEFD6FBFFD5CC51 (cited 12 Oct 2006). In: Australian Government Department of Industry Tourism and Resources,.

240.   World Health Organisation. The rational use of drugs. Report of the Conference of Experts, Nairobi 25-29 November 1985. Geneva: World Health Organisation; 1987.

241.   Barbour RS. The case for combining qualitative and quantitative approaches in health services research. J Health Serv Res Policy 1999;4:39-43.

242.   Runciman WB. Qualitative versus quantitative research - balancing cost, yield and feasibility. Qual Saf Health Care 2002;11:146-147.

243.   Reich MR. The politics of reforming health policies. Promot Educ 2002;9:138-142.

244.   Walley T, Earl-Slater A, Haycox A, Bagust A. An integrated national pharmaceutical policy for the United Kingdom? BMJ 2000;321:1523-1526.

245.   Mays N, Pope C. Qualitative Research In Health Care. London: BMJ Publishing Group; 1996.

246.   Patton MQ. Qualitative evaluation and evaluation methods. 3rd ed. Thousand Oaks, CA: Sage Publications; 2002.

247.   Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ 1995;311:42-45.

248.   Ritchie J, Lewis J. Qualitative research practice: a guide for social science students and researchers. London: Sage publications; 2003.

249.   Pope C, van Royen P, Baker R. Qualitative methods in research on healthcare quality. Qual Saf Health Care 2002;11:148-152.

250.   Fossey E, Harvey C, McDermott F, Davidson L. Understanding and evaluating qualitative research. Aust. N.Z J Psychiatry 2002;36:717-732.

251.   Sofaer S. Qualitative methods: what are they and why use them? Health Serv Res 1999;34:1101-1118.

252.   Pope C, Mays N. Qualitative research in health care. 2nd ed. London: BMJ Books; 2000.

253.   Mays N, Pope C. Qualitative research in health care: Assessing quality in qualitative research. BMJ 2000;320:50-52.

254.   Britten N. Qualitative research: qualitative interviews in medical research. BMJ 1995;311:251-253.

255.   Lindblad AK, Hartzema AG, Feltelius N. Patients' views of priority setting for new medicines. Scand J Rheumatol 2002;31:324-329.

256.   McDonald R, Burrill P, Walley T. Managing the entry of new medicines in the National Health Service: health authority experiences and prospects for primary care groups and trusts. Health and Social care in the Community 2001;9:341-347.

257.   Vuorenkoski L, Toivisinen H, Hemminki E. Drug reimbursement in Finland - a case of explicit prioritising in special categories. Health Policy 2003;66:169-177.

258.   Strauss A, Corbin J. Basics of qualitative research. 2nd Edition ed. California: SAGE; 1998.

259.   Pope C, Ziebland S, Mays N. Qualitative research in health care: Analysing qualitative data. BMJ 2000;320:114-116.

260.   Mays N, Pope C. Qualitative research: rigour and qualitative research. BMJ 1995;311:109-112.

261.   Lewis J, Ritchie J. Generalising from qualitative research. In: Ritchie J, Lewis J, editors. Qualitative research practice: A guide for social science students and researchers. London: SAGE; 2003. p. 336.

262.   Patton MQ. Enhancing the quality and credibility of qualitative analysis. Health Serv Res 1999;34:1189-1208.

263.   Nash P. Anti-tumor necrosis factor therapy: the Australian experience. APLAR Journal of Rheumatology 2006;9:119-123.

264.   Australian Government Department of Health and Ageing. Outcome statement of the Pharmaceutical Health And Rational use of Medicines (PHARM) committee meeting February 2006. Canberra: Australian Government Department of Health and Ageing; 2006.

265.   Lu CY, Williams KM, March LM, Bertouch J, Day RO. Subsidised access to TNFa inhibitors: is the rationale for exclusion of rheumatoid factor negative patients defensible? Med J Aust 2004;181:457-458.

266.   Sansom L. Subsidised access to TNFa inhibitors: is the rationale for exclusion of rheumatoid factor negative patients defensible? Med J Aust 2004;181:457-458.

267.   Morgan SG, McMahon M, Mitton C, Roughead E, Kanavos P, Menon D. Centralized drug review processes in Australia, Canada, New Zealand, and the United Kingdom. Health Aff (Millwood) 2006;25:337-347.

268.   Australian Government Department of Health and Ageing. Pharmaceutical Benefits Scheme - Public Summary Documents. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/public-summary-documents (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

269.   Consumers' Health Forum of Australia and Medicines Australia. Workshop Report: Guidelines for relationships between health consumer organisations and the pharmaceutical industry. Canberra: Consumers' Health Forum of Australia and Medicines Australia; 2005.

270.   Smith R. Transparency: a modern essential. BMJ 2004;328.

271.   Hill SR, Mitchell AS, Henry DA. Problems with the interpretation of pharmacoeconomic analyses: a review of submissions to the Australian Pharmaceutical Benefits Scheme. JAMA 2000;283:2116-2121.

272.   Australian Government Department of Health and Ageing. Working together to improve the Pharmaceutical Benefits Scheme - Review of post PBAC processes report. Canberra: Australian Government Department of Health and Ageing; 2004.

273.   Sculpher MJ. Shared decision making in a publicly funded health care system. Policies exist to reduce the risk of conflict between individual and society. BMJ 1999;319:725-726.

274.   Arnesen T, Fredriksen S. Coping with obligations towards patient and society: An empirical study of attitudes and practice among Norwegian physicians. J Med Ethics 1995;21:158.

275.   Coast J. Citizens, their agents and health care rationing: an exploratory study using qualitative methods. Health Econ 2001;10:159-74.

276.   Walley T. Drugs, money and society. Br J Clin Pharmacol 1995;39:343-345.

277.   Klein R. Priorities and rationing: pragmatism or principles? BMJ 1995;311:761-762.

278.   O'Donnell JL, Smyth D, Frampton C. Prioritizing health-care funding. Intern Med J 2005;35:409-412.

279.   Berkke M, Hjortdahl P, Kvien TK. Involvement and satisfaction: a Norwegian study of health care among 1,024 patients with rheumatoid arthritis and 1,509 patients with chronic noninflammatory musculoskeletal pain. Arthritis Rheum 2001;45:8-15.

280.   Garrity TF. Medical compliance and the clinician-patient relationship: a review. Soc Sci Med 1981;15:215-222.

281.   Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, et al. The impact of patient-centered care on outcomes. J Fam Pract 2000;49:796-804.

282.   Newby DA, Hill SR, Barker BJ, Drew AK, Henry DA. Drug information for consumers: should it be disease or medication specific? Results of a community survey. Aust N Z J Public Health 2001;25:564-570.

283.   Kiely PDW. Symptom concealment - a new phenomenon in patients treated with biological therapies? Rheumatology (Oxford) 2004;43:114-115.

284.   Gibson JL, Martin DK, Singer PA. Priority setting in hospitals: fairness, inclusiveness, and the problem of institutional power differences. Soc Sci Med 2005;61:2355-2362.

285.   Rat AC, Henegariu V, Boissier MC. Do primary care physicians have a place in the management of rheumatoid arthritis? Joint Bone Spine 2004;71:190-197.

286.   Henry DA, Kerridge I, Hill S, McNeill P, Doran E, Newby DA, et al. Medical specialists and pharmaceutical industry-sponsored research: a survey of the Australian experience. Med J Aust 2005;182:557-560.

287.   Breen K. The medical profession and the pharmaceutical industry: when will we open our eyes? Med J Aust 2004;180:409-410.

288.   Edmonds DJ, Dumbrell DM, Primrose JG, McManus P, Birkett DJ, Demirian V. Development of an Australian drug utilisation database: a report from the Drug Utilization Subcommittee of the Pharmaceutical Benefits Advisory Committee. Pharmacoeconomics 1993;3:427-432.

289.   McManus P, Marley J, Birkett DJ, Lindner J. Compliance with restrictions on the subsidized use of proton pump inhibitors in Australia. Br J Clin Pharmacol 1998;46:409-411.

290.   Australian Government Department of Health and Ageing. Portfolio Budget Statement 2005-06: Health Budget 2005-06. Canberra: Australian Government Department of Health and Ageing; 2005.

291.   West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. Am J Epidemiol 1995;142:1103-1112.

292.   Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50:619-625.

293.   Avorn J, Soumerai SB. Use of a computer-based Medicaid drug data to analyze and correct inappropriate medication use. J Med Syst 1982;6:377-386.

294.   Sena MM, Pashko S. Drug utilization review using a Medicaid claims database. Clin Ther 1993;15:900-904.

295.   Iezzoni LI. Assessing quality using administrative data. Ann Intern Med 1997;127:666-674.

296.   Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995;48:999-1009.

297.   Anderson GM, Beers MH, Kerluke K. Auditing prescription practice using explicit criteria and computerized drug benefit claims data. J Eval Clin Pract 1997;3:283-294.

298.   Bjerrum L, Rosholm JU, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. Eur J Clin Pharmacol 1997;53:7-11.

299.   Melnychuk D, Moride Y, Abenhaim L. Monitoring of drug utilization in public health surveillance activities: a conceptual framework. Can J Public Health 1993;84:45-49.

300.   Henry DA, Cully LR, Grigson T, Lee C. Recent trends in the prescribing of cholesterol lowering drugs in Australia. A report from the Drug Utilization Subcommittee of the Pharmaceutical Benefits Advisory Committee. Med J Aust 1991;155:332-336.

301.   Birkett DJ, Mitchell AS, Godeck A, Grigson T, Cully R, Lee C. Profiles of antibacterial drug use in Australia and trends from 1987 to 1989. A report from the Drug Utilization Subcommittee of the Pharmaceutical Benefits Advisory Committee. Med J Aust 1995;155:410-415.

302.   Peterson GM, Sugden JE. Educational program to improve the dosage prescribing of allopurinol. Med J Aust 1995;162:74-77.

303.   Breen CL, Degenhardt LJ, Bruno RB, Roxburgh AD, Jenkinson R. The effects of restricting publicly subsidised temazepam capsules on benzodiazepine use among injectiong drug users in Australia. Med J Aust 2004;181:300-304.

304.   O'Connell DL, Henry D, Tomlins R. Randomised controlled trial of effect of feedback on general practitioners' prescribing in Australia. BMJ 1999;318:507-511.

305.   Pearson SA, Ringland C, Lowinger J, Kelman C, Mant A. Using secondary data sources to evaluate the impact of the Joint Heart Failure Program on health outcomes: Report to the National Prescribing Service. Sydney: Population Health and Use of Medicines Unit, University of New South Wales; 2005.

306.   National Prescribing Service. NPS Evaluation Report No. 1 (June 2000). Sydney: National Prescribing Service; 2000.

307.   O'Sullivan C. Measuring health outcomes within the context of the National Medicines Policy: A discussion paper. Sydney, NSW: The Pharmaceutical Alliance; 2003.

308.   Australian Government Department of Health and Ageing. MediConnect. Available from: http://www.mediconnect.gov.au/index.htm (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

309.   Australian Government The Office of the Privacy Commissioner. Review of the Medicare and PBS Privacy Guidelines issued under section 135AA of the National Health Act 1953: Issues Paper. Canberra: Australian Government The Office of the Privacy Commissioner; 2004.

310.   Lazaridis EN. Database standardization, linkage, and the protection of privacy. Ann Intern Med 1997;127:696.

311.   Sibthorpe B, Kliewer E, Smith L. Record linkage in Australian epidemiological research: health benefits, privacy safeguards and future potential. Aust J Public Health 1995;19:250-256.

312.   Mount CD, Kelman CW, Smith LR, Douglas RM. An integrated electronic health record and information system for Australia? Med J Aust 2000;172:25-27.

313.   Kelman C, Pearson S, Day R, Holman CD, Kliewer E, Henry D. Evaluating medicines: let's use all the evidence. Med J Aust 2007;186:249-252.

314.   Holman CD, Bass AJ, Rouse IL, Hobbs MS. Population-based linkage of health records in Western Australia: development of a health services research linked database. Aust N Z J Public Health 1999;23:453-459.

315.   Kelman C, Smith L. It's time: record linkage--the vision and the reality. Aust N Z J Public Health 2000;24:100-101.

316.   Kelman CW, Bass AJ, Holman CD. Research use of linked health data--a best practice protocol. Aust N Z J Public Health 2002;26:251-255.

317.   Spilsbury K, Semmens JB, Saunders CM, Holman CD. Long-term survival outcomes following breast cancer surgery in Western Australia. ANZ J Surg 2005;75:625-630.

318.   Laurvick CL, Semmens JB, Leung YC, Holman CD. Ovarian cancer in Western Australia (1982-1998): trends in surgical intervention and relative survival. Gynecol Oncol 2003;88:141-148.

319.   Lawrence D, Holman CD, Jablensky AV, Fuller SA, Stoney AJ. Increasing rates of suicide in Western Australian psychiatric patients: a record linkage study. Acta Psychiatr Scand 2001;104:443-451.

320.   Lawrence D, Jablensky AV, Holman CD, Pinder TJ. Mortality in Western Australian psychiatric patients. Soc Psychiatry Psychiatr Epidemiol 2000;35:341-347.

321.   Kelman CW, Kortt MA, Becker NG, Li Z, Mathews JD, Guest CS, et al. Deep vein thrombosis and air travel: record linkage study. BMJ 2003;327:1072.

322.   Hall SE, Bulsara CE, Bulsara MK, Leahy TG, Culbong MR, Hendrie D, et al. Treatment patterns for cancer in Western Australia: does being Indigenous make a difference? Med J Aust 2004;181:191-194.

323.   Commonwealth Department of Education Science and Training. National Collaborative Research Infrastructure Strategy (NCRIS). Available from: http://www.dest.gov.au/sectors/research_sector/policies_issues_reviews/key_issues/ncris/default.htm (cited 12 Oct 2006). In: Commonwealth Department of Education Science and Training; 2005.

324.   Australian Rheumatology Association Database. Australian Rheumatology Association Database - A study of the long-term effects of arthritis and its treatments in Australia (Summary report, November 2005). Melbourne: Australian Rheumatology Association Database; 2005.

325.   Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. JAMA 1999;281:824-829.

326.   Moride Y, Haramburu F, Requejo AA, Begaud B. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol 1997;43:177-181.

327.   Goldman SA. Limitations and strengths of spontaneous reports data. Clin Ther 1998;20 Suppl C:C40-C44.

328.   Boyd IW. The role of the Australian Adverse Drug Reactions Advisory Committee (ADRAC) in monitoring drug safety. Toxicology 2002;181-182:99-102.

329.   Australian Government Department of Health and Ageing. Australian guideline for pharmacovigilance responsibilities of sponsors of registered medicines regulated by Drug Safety and Evaluation Branch - July 2003 Amended 31 May 2005. Canberra: Australian Government Department of Health and Ageing, Therapeutic Goods Administration; 2005.

330.   Gram LE, Hallas J, Andersen M. Pharmacovigilance based on prescription databases. Pharmacol Toxicol 2000;86 Suppl 1:13-15.

331.   Doran CM, Shakeshaft AP, Gates JA, Fawcett JE, Mattick RP. Current prescribing patterns of bupropion in Australia. Med J Aust 2002;177:162.

332.   Handelsman DJ. Trends and regional differences in testosterone prescribing in Australia, 1991-2001. Med J Aust 2004;181:419-422.

333.   Australian Government Health Insurance Commission. 2003-04 Annual Report. Canberra: Australian Government Health Insurance Commission; 2004.

334.   Robertson J, Fryer JL, O'Connell DL, Smith AJ, Henry DA. Limitations of Health Insurance Commission (HIC) data for deriving prescribing indicators. Med J Aust 2002;176:419-424.

335.   Australian Government Medicare Australia. Medicare Australia Service Charter Brochure. Available from: http://www.medicareaustralia.gov.au/ (cited 05 May 2007). In: Australian Government Medicare Australia.

336.   Australian Government Medicare Australia. Pharmaceutical Benefits Schedule item statistics. Available from: http://www.medicareaustralia.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml (cited 12 Oct 2006). In: Australian Government Medicare Australia.

337.   Australian Government Department of Health and Ageing. Australian Statistics on Medicines 2001-2002. Canberra: Australian Government Department of Health and Ageing; 2002.

338.   Australian Government Department of Health and Ageing. The Rural, Remote and Metropolitan Area (RRMA) classification system. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-workforce-bmp-rrma.htm (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

339.   Australian Institute of Health and Welfare. Rural, regional, remote health: a guide to remoteness classifications. AIHW cat no. PHE 53. Canberra: Australian Institute of Health and Welfare; 2004.

340.   Pincus T, Stein CM. Why randomized controlled clinical trials do not depict accurately long-term outcomes in rheumatoid arthritis: some explanations and suggestions for future studies. Clin Exp Rheumatol 1997;15:S27-S38.

341.   Wolfe F, Michaud K. Towards an epidemiology of rheumatoid arthritis outcome with respect to treatment: randomized controlled trials overestimate treatment response and effectiveness. Rheumatology (Oxford) 2005;44(Suppl 4):iv18-iv22.

342.   Drazen JM. COX-2 inhibitors - a lesson in unexpected problems. N Eng J Med 2005;352:1131-1132.

343.   Psaty BM, Furberg CD. COX-2 inhibitors - lessons in drug safety. N Eng J Med 2005;352:1133-1135.

344.   Australian Government Department of Health and Ageing. Australia New Zealand Therapeutic Products Authority (ANZTPA). Available from: http://www.tga.gov.au/tta/index.htm (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing,.

345.   European Medicines Agency (EMEA). ICH Topic E2E: Pharmacovigilance Planning (PVP). CPMP/ICH/5716/03. In: European Medicines Agency (EMEA); 2005.

346.   Camussi G, Albano E, Tetta C, Bussolino F. The molecular action of tumor necrosis factor-alpha. Eur J Biochem 1991;202:3-14.

347.   Genovese MC, Bathon JM, Fleischmann RM, Moreland LW, Martin RW, Whitmore JB, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol 2005;32:1232-1242.

348.   Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 2004;50:1051-1065.

349.   Fleischmann R, Stern R, Iqbal I. Etanercept - review of efficacy and safety after five years of clinical use. Therapy 2004;1:11-23.

350.   Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:889-894.

351.   Fleischmann RM, Tesser J, Schiff MH, Schechtman J, Burmester GR, Bennett R, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1006-1012.

352.   Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287-2293.

353.   Baecklund E, Askling J, Rosenquist R, Ekbom A, Klareskog L. Rheumatoid arthritis and malignant lymphomas. Curr Opin Rheumatol 2004;16:254-261.

354.   Solomon DH, Curhan GC, Rimm EB, Cannuscio CC, Karlson EW. Cardiovascular risk factors in women with and without rheumatoid arthritis. Arthritis Rheum 2004;50:3444-3449.

355.   Hyrich KL, Silman AJ, Watson KD, Symmons DPM. Anti-tumour necrosis factor-alpha therapy in rheumatoid arthritis: an update on safety. Ann Rheum Dis 2004;63:1538-1543.

356.   Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol 2003;30:36-40.

357.   Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford) 2003;42:617-621.

358.   Bieber J, Kavanaugh A. Tuberculosis and opportunistic infections: relevance to biologic agents. Clin Exp Rheumatol 2004;22:S126-S133.

359.   Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004;50:1740-1751.

360.   Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al. Arthritis Res Ther 2006;8:111.

361.   Strom BL. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons; 2005.

362.   Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996;11:1215-1218.

363.   Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342:1878-1886.

364.   Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Eng J Med 2000;342:1887-1892.

365.   Wolfe F, Michaud K. A brief introduction to the national data bank for rheumatoid diseases. Clin Exp Rheumatol 2005;23(Suppl 39):S168-S171.

366.   Kremer JM. The CORRONA database. Clin Exp Rheumatol 2005;23:S172-S177.

367.   Yazici Y. A database in private practice: the Brooklyn outcomes of arthritis rheumatology database. Clin Exp Rheumatol 2005;23(Suppl 39):S182-S187.

368.   Sokka T, Pincus T. An early rheumatoid arthritis treatment evaluation registry (ERATER) in the United States. Clin Exp Rheumatol 2005;23:S178-S181.

369.   Silman AJ, Symmons DPM, Scott DGI, Griffiths I. British Society for Rheumatology Biologics Register. Annals of Rheumatic Diseases 2003;62:ii28-ii29.

370.   Silman A, Symmons D, Scott DGI. BSR Biologics registry. Rheumatology (Oxford) 2004;43:1463-1464.

371.   Watson K, Symmons D, Griffiths I, Silman A. The British Society for Rheumatology Biologic Register. Ann Rheum Dis 2005;64:iv42-iv43.

372.   van Vollenhoven RF, Askling J. Rheumatoid arthritis registries in Sweden. Clin Exp Rheumatol 2005;23:S195-S200.

373.   Askling J, Fored CM, Geborek P, Jacobsson LTH, van Vollenhoven R, Feltelius N, et al. Swedish registers to address drug safety and clinical issues in rheumatoid arthritis. Ann Rheum Dis 2006;65:707-712.

374.   Gomez-Reino JJ, Carmona L, BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther 2006;8:R29.

375.   Hetland ML. DANBIO: a nationwide registry of biological therapies in Denmark. Clin Exp Rheumatol 2005;23:S205-S207.

376.   Langenegger T, Fransen J, Forster A, Seitz M, Michel BA. [Clinical quality management in rheumatoid arthritis]. Z Rheumatol 2001;60:333-341.

377.   Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis 2006;65:746-752.

378.   Kvien TK, Heiberg MS, Lie E, Kaufmann C, Mikkelsen K, Nordvag BY, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23:S188-S194.

379.   Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanove-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005;52:3403-3412.

380.   Zink A, Listing J, Kary S, Ramlau P, Stoyanove-Scholz M, Babinsky K, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 2005;64:1274-1279.

381.   Nordstrom DC, Konttinen L, Korpela M, Tiippana-Kinnunen T, Eklund K, Forsberg S, et al. Classic disease modifying anti-rheumatic drugs (DMARDs) in combination with infliximab. The Finnish experience. Rheumatol Int 2006;26:741-748.

382.   Sokka T. Rheumatoid arthritis databases in Finland. Clin Exp Rheumatol 2005;23:S201-S204.

383.   Horneff G, Schmeling H, Foeldvari I, Ganser G, Girschick HJ, Hospach T, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis 2004;63:1638-1644.

384.   Reid C, Meehan A, Owen A, Wlodarczyk J, Robb T, Hardy M, et al. The Bosentan Patient Registry. In: National Medicines Symposium; 2006; Canberra, Australia; 2006.

385.   National Institute for Health and Clinical Excellence. The clinical effectiveness and cost-effectiveness of new drug treatments for rheumatoid arthritis: etanercept and infliximab. London: NHS R&D HTA; 2001.

386.   National Institute for Health and Clinical Excellence. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. Available from: http://www.nice.org.uk/page.aspx?o=291165 (cited 12 Oct 2006). In: National Institute for Health and Clinical Excellence; 2006.

387.   Griffiths I, Silman A, Symmons D, Scott DGI. BSR biologics registry. Rheumatology (Oxford) 2004;43:1463-1464.

388.   Hyrich KL, Symmons DPM, Watson KD, Silman AJ. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:1786-1794.

389.   Hyrich KL, Watson KD, Silman AJ, Symmons DPM, The BSR Biologics Register. Predictors of response to anti-TNF therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2006;45:1558-1565.

390.   Hyrich K, Symmons D, Watson K, Silman A. Baseline comorbidity levels in biologic and standard DMARD treated patients with rheumatoid arthritis: results from a national patient register. Ann Rheum Dis 2006;65:895-898.

391.   Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:2368-2376.

392.   Hyrich KL, Symmons DP, Watson KD, Silman AJ. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. Arthritis Rheum 2006;54:2701-2702.

393.   Geborek P, Nitelius E, Noltorp S, Petri H, Jacobsson L, Larsson L, et al. Population based studies of biological antirheumatic drug use in southern Sweden: comparison with pharmaceutical sales. Ann Rheum Dis 2005;64:1805-1807.

394.   Feltelius N, Fored CM, Blomqvist L, Geborek P, Jacobsson LT, Lindblad S, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis 2005;64:246-252.

395.   Lunde AS, Lundeborg S, Lettenstrom GS, Thygesen L, Huebner J. The person-number systems of Sweden, Norway, Denmark, and Israel. Vital Health Stat 1980;2:1-59.

396.   Geborek P, Bladstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005;64:699-703.

397.   Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1414-1420.

398.   Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1421-1426.

399.   Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005;52:1986-1992.

400.   Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005;32:1213-1218.

401.   Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis 2004;63:4-10.

402.   Gulfe A, Geborek P, Saxne T. Response criteria for rheumatoid arthritis in clinical practice: how useful are they? Ann Rheum Dis 2005;64:1186-1189.

403.   Geborek P, Crnkic M, Petersson IF, Saxne T. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis 2002;61:793-798.

404.   van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis 2003;62:1195-1198.

405.   van Vollenhoven RF, Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effect. Ann Rheum Dis 2004;63:426-430.

406.   Lu CY, Williams KM, Day RO. Accessing health outcome data on high cost medicines in Australia. Med J Aust 2006;184:411-413.

407.   Henry DA, Hill SR, Harris A. Drug prices and value for money: the Australian Pharmaceutical Benefits Scheme. JAMA 2005;294:2630-2632.

408.   Australian Institute of Health and Welfare. Arthritis and musculoskeletal conditions in Australia, 2005 AIHW Cat. No. PHE67. Canberra: Australian Institute of Health and Welfare; 2005.

409.   Australian Rheumatology Association. Arthritis Specialists applaud PBS listing for new drug. Australian Rheumatology Association (Media Release), 4 July 2003. Available from: http://www.rheumatology.org.au/downloads/EnbrelMediaRelease.pdf (cited 06 March 2006). In: Australian Rheumatology Association; 2003.

410.   Yee CS, Filer A, Pace A, Douglas K, Situnayake D, Rowe IF. The prevalence of patients with rheumatoid arthritis in the West Midlands fulfilling the BSR criteria for anti-tumour necrosis factor therapy: an out-patient study. Rheumatology (Oxford) 2003;42:856-859.

411.   Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum 2003;48:313-318.

412.   Douglas K, Bowman SJ. How many patient are eligible for anti-TNF therapy in the UK? Rheumatology (Oxford) 2001;40:1416.

413.   Australian Government Department of Health and Ageing. PBS continues to make medicines affordable for all Australians (Media Release). Available from: http://www.health.gov.au/ (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing; 2004.

414.   Byron P, Zhao Y, Guthridge S, Brailsford R, Stacey F, Parkinson J. Medicare and Pharmaceutical Benefits Scheme Usage Patterns in the Northern Territory 1993/94 to 2003/04. Northern Territory: Commonwealth Department of Health and Community Services; 2005.

415.   Australian Bureau of Statistics. Population, Australian States and Territories - Electronic Delivery (December 2003) ABS Cat. No. 3239.0.55.001. Canberra: Australian Bureau of Statistics; 2003. Report No.: ABS Cat. No. 3239.0.55.001.

416.   Cush JJ. Biological drug use: US perspectives on indications and monitoring. Ann Rheum Dis 2005;64:iv18-iv23.

417.   Kvien TK, Uhlig T, Kristiansen S. Criteria for TNF-targeted therapy in rheumatoid arthritis. Drugs 2001;61:1711-1720.

418.   Pressman Lovinger S. Use of biologics for rheumatoid arthritis tempered by concerns over safety, cost. JAMA 2003;289:3229-3230.

419.   Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, MacFarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor-alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-1563.

420.   Gilbert TDJ, Smith D, Ollendorf DA. Patterns of use, dosing, and economic impact of biologic agent use in patients with rheumatoid arthritis: a retrospective cohort study. BMC Musculoskelet Disord 2004;14:36.

421.   Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. J Rheumatol 2004;31:1538-1545.

422.   Sidiropoulos P, Bertsias G, Kritikos HD, Kouroumali H, Voudouris K, Boumpas DT. Infliximab treatment for rheumatoid arthritis, with dose titration based on the Disease Activity Score: dose adjustments are common but not always sufficient to assure sustained benefit. Ann Rheum Dis 2004;63:144-148.

423.   van der Heijde DM. Overview of radiologic efficacy of new treatments. Rheum Dis Clin North Am 2004;30:285-293.

424.   Nurmohamed MT, Dijkmans BA. Efficacy, tolerability and cost effectiveness of disease-modifying antirheumatic drugs and biologic agents in rheumatoid arthritis. Drugs 2005;65:661-694.

425.   Perera LC, Tymms KE, Wilson BJ, Shadbolt B, Brook AS, Dorai Raj AK, et al. Etanercept in severe active rheumatoid arthritis: first Australian experience. Intern Med J 2006;36:625-631.

426.   Lipsky PE, van der Heijde DM, St. Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Eng J Med 2000;343:1594-1602.

427.   Klareskog L, Hvan der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-681.

428.   Oliver A, Mossialos E. Equity of access to health care: outlining the foundations for action. J Epidemiol Community Health 2004;58:655-658.

429.   Fretheimm A, Oxman AD. International variation in prescribing antihypertensive drugs: Its extent and possible explanations. BMC Health Serv Res 2005;5:21.

430.   Goodman B. Do drug company promotions influence physician behavior? West J Med 2001;174:232-233.

431.   Emery P, Buch M. Treating rheumatoid arthritis with tumour necrosis factor-alpha blockade: May be a giant therapeutic leap or a small expensive step. BMJ 2002;324:312-313.

432.   Buxton MJ. Economic Evaluation and Decision Making in the UK. Pharmacoeconomics 2006;24:1133-1142.

433.   Kay LJ, Griffiths ID. UK consultant rheumatologists' access to biological agents and views on the BSR Biologics Register. Rheumatology (Oxford) 2006;45:1376-1379.

434.   Yelin EH, Trupin LS, Katz PP. Impact of managed care on the use of biologic agents for rheumatoid arthritis. Arthritis Rheum 2005;53:423-430.

435. Sokol MC. Effective coverage and reimbursement strategies for etanercept and infliximab in the treatment of rheumatoid arthritis. Manag Care Interface 2005;18:32-37.

436. Titlow K, Randel L, Clancy CM, Emanuel EJ. Drug coverage decisions: the role of dollars and values. Health Aff (Millwood) 2000;19:240-247.

437. DeWitt EM, Glick HA, Albert DA, Joffe MM, Wolfe F. Medicare coverage of tumor necrosis factor alpha inhibitors as an influence on physicians' prescribing behavior. Arch Intern Med 2006;166:57-63.

438. Department of Health (United Kingdom). Variations in usage of cancer drugs approved by NICE: Report of the Review undertaken by the National Cancer Director. Available from: http://www.dh.gov.uk/ (cited 12 Oct 2006). In: Department of Health, United Kingdom; 2004.

439. Jacobson M, O'Malley AJ, Earle CC, Pakes J, Gaccione P, Newhouse JP. Does reimbursement influence chemotherapy treatment for cancer patients? Health Aff (Millwood) 2006;25:437-443.

440. Anis AH, Guh D, Wang XH. A dog's breakfast: prescription drug coverage varies widely across Canada. Med Care 2001;39:315-326.

441. Gregoire JP, MacNeil P, Skilton K, Moisan J, Menon D, Jacobs P, et al. Inter-provincial variation in government drug formularies. Can J Public Health 2001;92:307-312.

442. Menon D, Stafinski T, Stuart G. Access to drugs for cancer: does where you live matter? Can J Pub Health 2005;96:454-458.

443. McMahon M, Morgan S, Mitton C. The Common Drug Review: a NICE start for Canada? Health Policy 2006;77:339-351.

444. Sokka T. Work disability in early rheumatoid arthritis. Clin Exp Rheumatol 2003;21:S71-S74.

445. Pincus T. The underestimated long term medical and economic consequences of rheumatoid arthritis. Drugs 1995;50:1-14.

446. Kavanaugh A. Health economics: implications for novel antirheumatic therapies. Ann Rheum Dis 2005;64:iv65-iv69.

447. Lapsley HM, March LM, Tribe KL, Courtenay BG, Brooks PM. Living with rheumatoid arthritis: expenditures, health status, and social impact on patients. Ann Rheum Dis 2002;61:818-821.

448. Yelin E. The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. J Rheumatol Suppl 1996;44:47-51.

449. Callahan LF. The burden of rheumatoid arthritis: facts and figures. J Rheumatol 1998;53 Suppl:8-12.

450. Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. Rheumatology (Oxford) 2000;39:28-33.

451.   Armstrong DJ, McCausland EMA, Wright GD. The impact of anti-TNF-alpha therapy on the nature of service provision. Rheumatology (Oxford) 2006;45:112.

452.   Stenger AA, van Leeuwen MA, Houtman PM, Bryuyn GA, Speerstra F, Barendsen BC, et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol 1998;37:1157-1163.

453.   Egsmose C, Lund B, Borg G, Pettersson H, Berg E, Brodin U, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year follow-up of a prospective double blind placebo controlled study. J Rheumatol 1995;12:2208-2213.

454.   van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124:699-707.

455.   Mottonen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 2002;46:894-898.

456.   O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1164-1170.

457.   van Aken J, Lard LR, le Cessie S, Hazes JM, Breedveld FC, Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2004;63:274-279.

458.   Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Eng J Med 2000;343:1586-1593.

459.   Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443-1450.

460.   Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumour necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. Arthritis Rheum 2004;50:1400-1411.

461.   Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 2004;63:149-155.

462.   St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432-3443.

463.   Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.

464.   Breedveld FC, Han C, Bala M, van der Heijde D, Baker D, Kavanaugh AF, et al. Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. Ann Rheum Dis 2005;64:52-55.

465.   Bykerk VP, Keystone EC. What are the goals and principles of management in the early treatment of rheumatoid arthritis? Best Pract Res Clin Rheumatol 2005;19:147-161.

466.   Gibson PR, Iser J. Inflammatory bowel disease. Aust Fam Physician 2005;34:233-237.

467.   Australian Bureau of Statistics. 3105.0.65.001 - Australian Historical Population Statistics. ABS Cat. No. 3239.0.55.001. Available from: http://www.abs.gov.au (cited 12 Oct 2006). In: Australian Bureau of Statistics.

468.   Australian Government Department of Health and Ageing. Health Priorities. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/Health+Priorities-1 (cited 12 Oct 2006). In: Australian Government Department of Health and Ageing.

469.   Australian Government Department of Health and Ageing. Schedule of Pharmaceutical Benefits. Available from: www.pbs.gov.au/ (cited 27 Apr 2007). In: Australian Government Department of Health and Ageing.

470.   Donnelly N, McManus P, Dudley J, Hall W. Impact of increasing the re-supply interval on the seasonality of subsidised prescription use in Australia. Aust N Z J Public Health 2000;24:603-606.

471.   Eberhardt K, Rydgren L, Fex E, Svensson B, Wollheim FA. D-penicillamine in early rheumatoid arthritis: experience from a 2-year double blind placebo controlled study. Clin Exp Rheumatol 1996;14:625-631.

472.   Chan V, Tett SE. Changes in use of disease-modifying anti-rheumatic drugs in Australia over the period 1992-2004. Pharmacoepidemiol Drug Saf 2006:462-468.

473.   Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381-3390.

474.   Godinho F, Godfrin B, El Mahou S, Navaux F, Zabraniecki L, Cantagrel A. Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis. Clin Exp Rheumatol 2004;22:328-330.

475.   Hansen KE, Cush J, Singhal A, Cooley DA, Cohen S, Patel SR, et al. The safety and efficacy of leflunomide in combination with infliximab in rheumatoid arthritis. Arthritis Rheum 2004;51:228-232.

476.   O'Dell JR, Petersen K, Leff R, Palmer W, Schned E, Blakely K, et al. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol 2006;33:213-218.

477.   Finckh A, Simard JF, Duryea J, Liang MH, Huang J, Daneel S, et al. The effectiveness of anti-tumor necrosis factor therapy in preventing progressive radiographic joint damage in rheumatoid arthritis. Arthritis Rheum 2006;54:54-59.

478.   Australian Government Department of Health and Ageing. Health and Ageing Factbook 2006. Canberra: Australian Government Department of Health and Ageing; 2006.

479.   Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27:299-309.

480.   Andersson K, Petzold MG, Sonesson C, Lonnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trends in Sweden 1986-2002. Health Policy 2006;79:231-243.

481.   Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, Van Staa TP, et al. The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology (Oxford) 2005;44:1394-1398.

482.   Zink A. Practice variation in the treatment of rheumatoid arthritis among German rheumatologists. J Rheumatol 2001;28:2201-2208.

483.   Carli C, Ehlin AGC, Klareskog L, Lindblad S, Montgomery SM. Trends in DMARD prescription in early rheumatoid arthritis are influenced more by hospital setting than patient or disease characteristics. Ann Rheum Dis 2006;65:1102-1105.

484.   Daniels N, Sabin JE. Settings limits fairly: can we learn to share medical resources? Oxford: Oxford University Press; 2002.

485.   Mill JS. Utilitarianism. Indianapolis: Bobbs-Merrill; 1957.

486.   Kelly PJ. Utilitarianism and distributive justice: Jeremy Bentham and the Civil Law. Oxford: Clarendon Press; 1990.

487.   Harris J. Justice and equal opportunities in health care. Bioethics 1999;13:392-404.

488.   Stein MS. The distribution of life-saving medical resources: equality, life expectancy, and choice behind the veil. Soc Philos Policy 2002;19:212-245.

489.   Nord E. Concerns for the worse off: fair innings versus severity. Soc Sci Med 2005;60:257-263.

490.   Mitton C, Donaldson C. Resource allocation in health care: health economics and beyond. Health Care Anal 2003;11:245-257.

491.   Williams-Jones B, Burgess MM. Social Contract Theory and Just Decision Making: Lessons from Genetic Testing for the BRCA Mutations. Kennedy Inst Ethics J 2004;14:115-186.

492.   Daniels N, Sabin J. The ethics of accountability in managed care reform. Health Aff (Millwood) 1998;17:50-64.

493.   Evidence based medicine working group (EBM). Evidence based medicine: a new approach to teaching the practice of medicine. JAMA 1992;268:420-425.

494.   Biller-Andorno N, Lie RK, ter Meulen R. Evidence-based medicine as an instrument for rational health policy. Health Care Anal 2002;10:261-275.

495.   Kerridge I, Lowe M, Henry D. Ethics and evidence based medicine. BMJ 1998;316:151-153.

496.   Hope T. Evidence based medicine and ethics. J Med Ethics 1995;21:259-260.

497.   Saarni SI, Gylling HA. Evidence based medicine guidelines: a solution to rationing or politics disguised as science? J Med Ethics 2004;30:171-175.

498.   Sackett DL, Rosenburg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71-72.

499.   McElwee NE, Ho SY, McGuigan KA, Horn ML. Evidence-based coverage decisions? Primum non nocere. Health Aff (Millwood) 2006;25:W279-W282.

500.   Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol 2003;30:1138-1146.

501.   Morrow RH, Bryant JH. Health Policy Approaches to Measuring and Valuing Human Life: Conceptual and Ethical Issues. Am J Public Health 1995;85:1356-1360.

502.   Berghmans R, Berg M, van den Burg M, ter Meulen R. Ethical issues of cost effectiveness analysis and guideline setting in mental health care. J Med Ethics 2004;30:146-150.

503.   Hill S. Transparency in economic evaluations. Pharmacoeconomics 2005;23:967-969.

504.   Maetzel A. Cost-effectiveness analysis: out of touch with clinical reality? Arthritis Rheum 2005;53:3-4.

505.   Ham C, Robert G. Reasonable Rationing: International Experience of Priority Setting in Health Care. Maidenhead: Open University Press; 2003.

506.   Greenhalgh T, Kostopoulou O, Harries C. Making decisions about benefits and harms of medicines: Even when good scientific data are available, people's interpretation of risks and benefits will differ. BMJ 2004;329:47-50.

507.   Dobrow MJ, Goel V, Upshur REG. Evidence-based health policy: context and utilisation. Soc Sci Med 2004;58:207-217.

508.   Plsek P, Greenhalgh T. Complexity science: the challenge of complexity in health care. BMJ 2001;323:625-628.

509.   Drummond M. Prioritizing investments in health: can we assess potential value for money? J Rheumatol 2003;30 Suppl 68:19-20.

510.   George B, Harris A, Mitchell A. Cost-effectiveness analysis and the consistency of decision making: evidence from pharmaceutical reimbursement in Australia (1991 to 1996). Pharmacoeconomics 2001;19:1103-1109.

511.   Donald F, Ward MM. Evaluative laboratory testing practices of United States rheumatologists. Arthritis Rheum 1998;41:725-729.

512.   Dawes PT, Fowler PD, Clarke S, Fisher J, Lawton A, Shadforth MF. Rheumatoid arthritis: treatment which controls the C-reactive protein and erythrocyte sedimentation rate reduces radiological progression. Br J Rheumatol 1986;25:44-49.

513.   van Leeuwen MA, van der Heijde DM, van Rijswijk MH, Houtman PM, van Riel PL, van de Putte LB, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J Rheumatol 1994;21:425-429.

514.   Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis Rheum 2001;44:1736-1743.

515.   Buch MH, Seto Y, Bingham SJ, Bejarano V, Bryer D, White J, et al. C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: Defining subtypes of nonresponse and subsequent response to etanercept. Arthritis Rheum 2005;52:42-48.

516.   Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. Arthritis Rheum 1998;41:1571-1582.

517.   Coste J, Spira A, Clerc D, Paolaggi JB. Prediction of articular destruction in rheumatoid arthritis: disease activity markers revisited. J Rheumatol 1997;24:28-34.

518.   van Leeuwen MA, van Rijswijk MH, Sluiter WJ, van Riel PL, Kuper IH, van de Putte LB, et al. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. J Rheumatol 1997;24:20-27.

519.   Sokka T, Pincus T. Quantitative joint assessment in rheumatoid arthritis. Clin Exp Rheumatol 2005;23:S58-S62.

520.   van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916-920.

521.   van der Heijde DM, van 't Hof MA, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579-581.

522.   Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol 2005;23:S93-S99.

523.   Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729-740.

524.   Scott DL, Antoni C, Choy EH, Van Riel PC. Joint counts in routine practice. Rheumatology (Oxford) 2003;42:919-923.

525.   American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum 1996;39:723-731.

526.   Scott DL, Smith C, Kingsley G. Joint damage amd disability in rheumatoid arthritis: an updated systematic review. Clin Exp Rheumatol 2003;21:S20-S27.

527.   Landewe R, van der Heijde D. Radiographic progression in rheumatoid arthritis. Clin Exp Rheumatol 2005;23:S63-S68.

528.   Smart JJC, Williams B. Utilitarianism: For and against. Cambridge: Cambridge University Press; 1973.

529.   Williams RC. Rheumatoid factors: historical perspective, origins and possible role in disease. J Rheumatol 1992;19:42-45.

530.   Soltys AJ, Sutton BJ. Rheumatoid factors: where are we now? Ann Rheum Dis 1997;56:285-286.

531.   Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-324.

532.   Wolfe F, Cathey MA, Roberts FK. The latex test revisited. Rheumatoid factor testing in 8,287 rheumatic disease patients. Arthritis Rheum 1991;34:951-960.

533.   Kim JM, Weisman MH. When does rheumatoid arthritis begin and why do we need to know? Arthritis Rheum 2000;43:473-484.

534.   Green MJ, Marzo-Ortega H, McGonagle D, Wakefield RJ, Proudman S, Conaghan PG, et al. Persistence of mild, early inflammatory arthritis - the importance of disease duration, rheumatoid factor, and the shared epitope. Arthritis Rheum 1999;42:2184-2188.

535.   Gough A, Faint J, Salmon M, Hassell A, Wordsworth P, Pilling D, et al. Genetic typing of patients with inflammatory arthritis at presentation can be used to predict outcome. Arthritis Rheum 1994;37:1166-1170.

536.   Paimela L, Palosuo T, Leirisalo-Repo M, Helve T, Aho K. Prognostic value of quantitative measurement of rheumatoid factor in early rheumatoid arthritis. Br J Rheumatol 1995;34:1146-1150.

537.   Listing J, Rau R, Muller B, Alten R, Czerwony G, Gromnica-Ihle E, et al. HLA-DRB1 genes, rheumatoid factor, and elevated C-reactive protein: independent risk factors of radiographic progression in early rheumatoid arthritis. J Rheumatol 2000;27:2100-2109.

538.   Moreland LW, Margolies G, Heck LWJ, Saway A, Blosch C, Hanna R, et al. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. J Rheumatol 1996;23:1849-1855.

539.   Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Eng J Med 1997;337:141-147.

540.   Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Eng J Med 1999;340:253-259.

541.   Keystone EC, Schiff MH, Kremer JM, Kafka S, Lovy M, DeVries T. Once-weekly administration of 50mg etanercept in patients with active rheumatoid arthritis - results of a multicentre, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2004;50:353-363.

542.   Elliott M, Maini R, Feldmann M, Kalden JR, Antoni C, Smolen JS. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrois factor-alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;334:1105-1110.

543.   Kavanaugh A, St. Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric Anti-tumor necrosis factor-alpha monocloncal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol 2000;27:841-850.

544.   Shergy WJ, Isern RA, Cooley DA, Harshbarger JL, Huffstutter JE, Hughes GM, et al. Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis. J Rheumatol 2002;29:667-677.

545.   den Broeder A, van de Putte L, Rau R, Schattenkirchner M, Van Riel P, Sander O, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol 2002;29:2288-2298.

546.   Kempeni J. Preliminary results of early clinical trials with the fully human anti-TNF-alpha monoclonal antibody D2E7. Ann Rheum Dis 1999;58:i70-i72.

547.   Kempeni J. Update on D2E7: a fully human anti-tumour necrosis factor-alpha monoclonal antibody. Ann Rheum Dis 2000;59:i44-i45.

548.   Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther 2003;25:1700-1721.

549.   van de Putte LB, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis 2003;62:1168-1177.

550.   FDA. Clinical review for Humira (adalimumab) BLA 125057. United States: Food and Drug Administration (FDA); 2004.

551.   van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508-516.

552.   Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30:2563-2571.

553.   FDA. Clinical review for Enbrel (etanercept). United States: Food and Drug Administration (FDA); 1998.

554.   Bigger JT. Issues in subgroup analyses and meta-analyses of clinical trials. J Cardiovasc Electrophysiol 2003;14:s6-s8.

555.   Rothwell PM. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005;365:176-186.

556.   Cook DI, Gebski VJ, Keech AC. Subgroup analysis in clinical trials. Med J Aust 2004;180:289-291.

557.   Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis - the importance of disease duration. Arthritis Rheum 2000;43:22-29.

558.   Mann EL. Subsidised access to TNF-alpha inhibitors: is the rationale for exclusion of rheumatoid factor negative patients defensible? Med J Aust 2005;182:47-48.

559.   van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845-1850.

560.   Ranganathan P. Pharmacogenomics of tumor necrosis factor antagonists in rheumatoid arthritis. Pharmacogenomics 2005;6:481-490.

561.   Gorman JD, Lum RF, Chen JJ, Suarez-Almazor M, Thomson G, Criswell LA. Impact of shared epitope genotype and ethnicity on erosive disease: a meta-analysis of 3,240 rheumatoid arthritis patients. Arthritis Rheum 2004;50:400-412.

562.   O'Dell JR, Nepom B, Haire C, Gersuk VH, Gaur L, Moore GF, et al. HLA-DRB1 typing in rheumatoid arthritis: predicting response to specific treatments. Ann Rheum Dis 1998;57:209-213.

563.   Mugnier B, Balandraud N, Darque A, Roudier C, Roudier J, Reviron D. Polymorphism at position -308 of the tumor necrosis factor-alpha gene influences outcome of infliximab therapy in rheumatoid arthritis. Arthritis Rheum 2003;48:1849-1852.

564.   Padyukov L, Lampa J, Heimburger M, Ernestam S, Cederholm T, Lundkvist I, et al. Genetic markers for the efficacy of tumour necrosis factor blocking therapy in rheumatoid arthritis. Ann Rheum Dis 2003;62:526-529.

565.   La Caze A. Does pharmacogenomics provide an ethical challenge to the utilisation of cost-effectiveness analysis by public health systems? Pharmacoeconomics 2005;23:445-447.

566.   Bala MV, Zarkin GA. Pharmacogenomics and the evolution of healthcare: is it time for cost-effectiveness analysis at the individual level? Pharmacoeconomics 2004;22:495-498.

567.   Clayton EW. Ethical, legal, and social implications of genomic medicine. N Eng J Med 2003;349:562-569.

568.   Green JM, Hewison J, Bekker HL, Bryant LD, Cuckle HS. Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review. Health Technol Assess 2004;8:1-109.

569.   Harris M, Winship I, Spriggs M. Controversies and ethical issues in cancer-genetics clinics. Lancet Oncol 2005;6:301-310.

570.   FDA. Guidance for industry: Pharmacogenomic data submissions. United States: Food and Drug Administration (FDA), Center for Drug Evaluation and Research; 2005.

571.   Daniels N. Accountability for reasonableness. BMJ 2000;321:1300-1301.

572.   Levinson W, Laupacis A. A call for fairness in formulary decisions. Arch Intern Med 2006;166:16-18.

573.   Lofgren H, Boer R. Pharmaceuticals in Australia: developments in regulation and governance. Soc Sci Med 2004;58:2397-2407.

574.   Brocq O, Plubel Y, Breuil V, Grisot C, Flory P, Mousnier A, et al. Etanercept-infliximab switch in rheumatoid arthritis 14 out of 131 patients treated with anti TNFalpha. Press Med 2002;31:1836-1839.

575.   Ang H, Helfgott S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumor necrosis factor-apha antagonists in patients with rheumatoid arthritis? J Rheumatol 2003;30:2315-2318.

576.   Gomez-Puerta JA, Sanmarti R, Rodriguez-Cros JR, Canete JD. Etanercept is effective in patients with rheumatoid arthritis with no response to infliximab therapy. Ann Rheum Dis 2004;63:896.

577.   Sanmarti R, Gomez-Puerta JA, Rodriguez-Cros JR, Albaladejo C, Munoz-Gomez J, Canete JD. Etanercept in rheumatoid arthritis patients with a poor therapeutic response to infliximab. Med Clin (Barc) 2004;122:321-324.

578.   Hansen KE, Hildebrand JP, Genovese MC, Cush JJ, Patel S, Cooley DA, et al. The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. J Rheumatol 2004;31:1098-1102.

579.   Haraoui B, Keystone EC, Thorne JC, Pope JE, Chen I, Asare CG, et al. Clinical outcomes of patients with rheumatoid arthritis after switching from infliximab to etanercept. J Rheumatol 2004;31:2356-2359.

580.   Favalli EG, Arreghini M, Arnoldi C, Panni B, Marchesoni A, Tosi S, et al. Anti-tumour necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. Arthritis Rheum 2004;51:301-302.

581.   Yazici Y, Erkan D. Do etanercept-naive patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed? Ann Rheum Dis 2004;63:607-612.

582.   Wick MC, Ernestam S, Lindblad S, Bratt J, Klareskog L, van Vollenhoven RF. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. Scand J Rheumatol 2005;34:353-358.

583.   Cohen G, Courvoisier N, Cohen JD, Zaltni S, Sany J, Combe B. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. Clin Exp Rheumatol 2005;23:795-800.

584.   Bennett AN, Peterson P, Zain A, Grumley J, Panayi G, Kirkham B. Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. Rheumatology (Oxford) 2005;44:1026-1031.

585.   Nikas SN, Voulgari PV, Alamanos Y, Papadopoulos CG, Venetsanopoulou A, Georgiadis AN, et al. Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study. Ann Rheum Dis 2006;65:257-260.

586.   Sawyer LM. Community participation: lip service? Nurs Outlook 1995;43:17-22.

587.   Litva A, Coast J, Donovan J, Eyles J, Shepherd M, Tacchi J, et al. 'The public is too subjective': public involvement at different levels of health-care decision making. Soc Sci Med 2002;54:1825-1837.

588. Culyer AJ. Involving stakeholders in healthcare decisions - the experience of the National Institute for Health and Clinical Excellence (NICE) in England and Wales. Healthc Q 2005;8:56-60.

589. Mooney GH, Blackwell SH. Whose health service is it anyway? Community values in healthcare. Med J Aust 2004;180:76-78.

590. Sabin JE, Daniels N. Making insurance coverage for new technologies reasonable and accountable. JAMA 1998;279:703-704.

591. Wailoo A, Anand P. The nature of procedural preferences for health-care rationing decisions. Soc Sci Med 2005;60:223-236.

592. Smith MD, Ahern MJ. Pharmaceutical Benefits Scheme criteria for the use of tumour necrosis factor inhibitors in the treatment of ankylosing spondylitis in Australia: are they evidence based? Intern Med J 2006;36:72-76.

593. Cookson R. ASTEC-Non-EU Case Study on Australia. Norwick: The London School of Economics and Political Science; 2000.

594. Henry DA, Birkett DJ. Changes to the Pharmaceutical Benefits Advisory Committee. Med J Aust 2001;174:209-10.

595. Harvey K, Faunce T, Lokuge B, Drahos P. Will the Australia-United States Free Trade Agreement undermine the Pharmaceutical Benefits Scheme? Med J Aust 2004;181:256-259.

596. Outterson MK. Free trade in pharmaceuticals. Med J Aust 2004;181:260-261.

597. Sansom L. Transparency and the Pharmaceutical Benefits Advisory Committee. Comment on Professor M.J. Eadie's editorial 'The secrecy of drug regulatory information'. Aust Prescr 2002;25:103-104.

598. Editorial Executive Committee of Australian Prescriber. Transparency - in the eye of the beholder. Aust Prescr 2005;28:83-84.

599. Marley J. Cost-effectiveness: the need to know. Aust Prescr 1996;19:58-59.

600. Madden S, Martin DK, Downey S, Singer PA. Hospital priority setting with an appeals process: a qualitative case study and evaluation. Health Policy 2005;73:10-20.

601. Australian National Audit Office. The Auditor-General Audit Report No. 12, 1997-98: Peformance Audit - Pharmaceutical Benefits Scheme, Department of Health and Family Services. Available from: http://www.anao.gov.au/ (cited 12 Oct 2006). In: Australian National Audit Office; 1997.

602. Devlin N, Parkin D, Gold M. WHO evaluates NICE. BMJ 2003;327:1061-1062.

603. Cookson R, McDaid D, Maynard A. Wrong SIGN, NICE mess: is national guidance distorting allocation of resources? BMJ 2001;323:743-745.

604. Mitton CR, McMahon M, Morgan S, Gibson J. Centralized drug review processes: are they fair? Soc Sci Med 2006;63:200-211.

605.   Pearson S, Rawlins MD. Quality, innovation, and value for money: NICE and the British National Health Service. JAMA 2005;294:2618-2622.

606.   National Institute for Health and Clinical Excellence (NICE). Guide to the Technology Appraisal Process (reference N0514). London: NHS R&D HTA; 2004.

607.   Rodgers AT. The National Institute for Clinical Excellence (NICE). Ann Rheum Dis 2002;61:ii92-ii95.

608.   National Institute for Health and Clinical Excellence (NICE). The guideline development process: an overview for stakeholders, the public and the NHS (reference number N1233). London: NHS R&D HTA; 2007.

609.   Bryan S, Williams I, McIver S. Seeing the NICE side of cost-effectiveness analysis: a qualitative investigation of the use of CEA in NICE technology appraisals. Health Econ 2007;16:179-193.

610.   Kmietowicz Z. NICE hears appeals over dementia drugs. BMJ 2006;333:165.

611.   Daniels N. Toward ethical review of health system transformations. Am J Public Health 2006;96:447-451.

612.   Culyer AJ. Equity - some theory and its policy implications. J Med Ethics 2001;27:275-283.

613.   McKneally MF, Dickens BM, Meslin EM, Singer PA. Bioethics for Clinicians: 13. Resource allocation. CMAJ 1997;157:163-167.

614.   Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. Milbank Q 2004;82:661-687.

615.   Glasziou PP. Support for trials of promising medications through the Pharmaceutical Benefits Scheme. A proposal for a new authority category. Med J Aust 1995;162:33-36.

616.   Medicines Australia. Code of Conduct. Available from: http://www.medicinesaustralia.com.au/pages/page5.asp (cited 12 May 2007). In: Medicines Australia.

617.   Campbell DT, Stanley JC. Experimental and quasi-experimental designs for research. 3rd ed. Boston: Houghton Mifflin Company; 1963.

618.   Ross-Degnan D, Soumerai SB, Fortess EE, Gurwitz JH. Examining product risk in context. Market withdrawal of zomepirac as a case study. JAMA 1993;270:1937-1942.

LIST OF APPENDICES

Appendix 3.1

Invitation to participate in the interview study

Address XXX

Research study: Exploring stakeholders' perceptions of subsidized access to tumour necrosis factor (TNF-alpha) inhibitors in Australia

Chief Investigator: Prof Ric Day   Co-Researcher: Christine Lu

Dear XXX

Invitation to participate in an interview discussion

Access to new, effective medicines is becoming increasingly problematic due to increasing consumer expectations and substantive resource constraints as the cost of healthcare continues to rise. Appropriate access is further complicated by the uncertainty of the long-term safety and high cost of the majority of these drugs. Representative of this problem is the new class of tumour necrosis factor (TNF-alpha) inhibitors for the treatment rheumatoid arthritis (RA). The TNF inhibitors that are subsidized by the Pharmaceutical Benefits Scheme in Australia are etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira).

We are currently conducting a research project, the aim is to examine the current arrangements of access to the TNF inhibitors via the Pharmaceutical Benefits Scheme. As part of the project, we would like to explore attitudes, perceptions, concerns, problems and solutions regarding these access arrangements. We will be conducting interviews with individuals who have different roles, and represent different stakeholder groups.

The interview will take approximately 45-60 minutes, at an appropriate location and time that is convenient to you. The interview will be recorded with your consent, information collected during the interview will be confidential.

If you decide to participate or would like to know more about this research study, please contact Christine Lu (phone 02-83822199, fax: 02-83822724, email: christine.lu@student.unsw.edu.au).

Your participation will be greatly appreciated, and may lead to an enhanced understanding of access to new medicines for the Australian community. We thank you in anticipation for considering this request.

Participation information will be forwarded to you prior to the interview.

Yours sincerely,

Christine Lu   Prof Ric Day
PhD Student   Chief Investigator

Appendix 3.2

Invitation to participate in the interview study (patient version)

Date

Address XXX

Research study: Exploring stakeholders' perceptions of subsidized access to tumour necrosis factor (TNF-alpha) inhibitors in Australia

Chief Investigator: Prof Ric Day   Co-Researcher: Christine Lu

Dear XXX

Invitation to participate in an interview discussion

Are you taking **Enbrel, Remicade, or Humira** (etanercept, infliximab, or adalimumab) for rheumatoid arthritis currently? Have you taken any of these medicines previously? Have you considered or are you applying to start on any of these medicines?

If you answered **YES** to any of the questions above, we would like to invite you to discuss your experiences with these medicines. Your views are important, and they need to be heard.

The interview will take about one hour, at an appropriate location and time that is convenient to you. If you agree, the interview will be sound recorded. What you say is strictly confidential.

If you wish to share your experiences and views, please contact Christine Lu (phone 02-83822199, fax: 02-83822724, email: christine.lu@student.unsw.edu.au).

Medicines are very important for improving the health and quality of life of individuals with on-going medical conditions, including rheumatoid arthritis. Your participation will contribute to a better understanding of how to make medicines available and affordable for the Australian community.

We thank you in anticipation for considering this request. Participation information will be provided to you before the interview.

Yours sincerely,

Christine Lu   Prof Ric Day

PhD Student   Rheumatologist/Clinical Pharmacologist

Appendix 3.3

Participant Information Sheet

Research study: Exploring stakeholders' perceptions of subsidized access to tumour necrosis factor (TNF-alpha) inhibitors in Australia

Chief Investigator: Prof Ric Day
Co-Researchers: Christine Lu

The tumour necrosis factor (TNF-alpha) inhibitors, etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira) are new treatments for rheumatoid arthritis subsidized by the Pharmaceutical Benefits Scheme under strict criteria. The aim of this research study is to examine your 'experience' with the arrangements of access to these medicines, and to enhance an understanding of the strengths and weaknesses and possible improvements in the access to these medicines. You have been selected as a possible participant for this study. Findings from the study will improve our understanding of appropriate access to and the utilisation of these medicines in Australia. This study is being conducted by Christine Lu as part of a PhD research programme in Clinical Pharmacology, under the supervision of Professor Ric Day and Associate Professor Ken Williams.

If you decide to take part in this study, you will participate in one interview of approximately 45-60 minutes. The interview will take place at an appropriate location and time that is convenient to you. The interview will be recorded using a digital sound recorder so that we can enure that all of your thoughts are noted. Hand-written notes may also be taken. You may withdraw from the study at the time of the interview. You will also be given the opportunity to review the interview transcript before it is used for data analysis.

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or except as required by law. If you give us your permission by signing the consent form, it is our plan that the findings of the study will be reported as part of a PhD thesis, and will be published in a peer-reviewed journal, and presented at conferences. In any publication, information will be provided in such a way that you cannot be identified.

If you have any questions about your rights as a research participant, please contact,

Executive Officer, St Vincent's Hospital Research Ethics Committee (phone 8382 2075, fax

8382 3667).

Participation in this study is entirely voluntary: you are not obliged to participate and if you do participate, you can withdraw at any time. There are no adverse consequences attached to either participating or withdrawing at any stage from the study.

When you have read this information, Christine Lu will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please contact Christine Lu on 8382 2199 or Prof Ric Day on 8382 2331.

This information sheet is for you to keep.

Appendix 3.4

Participant Consent Form

Research study: Exploring stakeholders' perceptions of subsidized access to tumour necrosis factor (TNF-alpha) inhibitors in Australia

Chief Investigator: Prof Ric Day
Co-Researchers: Christine Lu

I, ...
[name]

of ....
[address]

1. I acknowledge that I have read the *Participant Information Statement*, which explains why I have been selected, and the aims of the research study.
2. I am aware of the procedures involved in the study, including any inconvenience, discomfort, and of their implications.
3. I have been given the opportunity of asking any questions relating to this study and I have received satisfactory answers.
4. I freely choose to participate in this study and understand that I can withdraw without compromise at any time.
5. I understand that research data gathered from the study may be published, provided that I cannot be identified.
6. I hereby give permission to the researchers to use a digital sound recorder to record the discussion and understand that my personal information will remain confidential.
7. I acknowledge receipt of a copy of this Consent Form and the Participant Information Statement.
8. I hereby agree to participate in this research study.

Signature:...

Name: ....

Date: ....

Signature of witness:...

Name of witness:...

If you would like to know more about this research study at any stage, please contact Christine Lu on (02) 83822199 or Prof Ric Day on (02) 83822331. Any person with concerns or complaints about the conduct of a research study can contact the Executive Officer, St Vincent's Hospital Research Ethics Committee DARLINGHURST 2010 AUSTRALIA (Phone 02-83822075, Fax 02-83823667).

Appendix 3.5

Self-completed Questionnaire

Research study: Exploring stakeholders' perceptions of subsidized access to tumour necrosis factor (TNF-alpha) inhibitors in Australia

The purpose of this questionnaire is to provide a context for your perceptions on the arrangements of access to TNF inhibitors in Australia via the PBS, which will be explored in further detail in a subsequent interview. The questionnaire is expected to take approximately five minutes to complete. Your privacy related to participating in this study will be maintained at all times. The information you provide in this questionnaire will be identifiable by numerical code only. If you have any questions, please contact Christine Lu on 02-8382 2199 or Prof Ric Day on 02-8382 2331.

Please complete the questions below:

1. Demographics
(a) Age
- ❑ 18 to 29
- ❑ 30 to 39
- ❑ 40 to 49
- ❑ 50 to 59
- ❑ over 60

(b) Gender
- ❑ F
- ❑ M

2. Representation

Which of the following best describe the stakeholder group you represent and your current role?

Please tick one box

- ❑ Rheumatologist
- ❑ HIC manager/administrators
- ❑ PBAC member
- ❑ Pharmaceutical industry (marketing)
- ❑ Pharmaceutical industry (medical)
- ❑ Consumer organisation (AFA)
  Role (*Please indicate*): ………………
- ❑ Patient (both the initiating and continuing of treatment applications were approved)
- ❑ Patient (initiating of treatment – application was NOT approved)
- ❑ Patient (continuing of treatment – application was NOT approved)
- ❑ Others …………………………………………………

3. Involvement in the decision-making process led to listing of TNF inhibitors

Have you ever been a member or held an advisory position in the following:
Please tick one box for each question.
(i) Australian Rheumatology Association therapeutics committee?

❑ Yes ❑ No

(ii) PBAC? ❑ Yes ❑ No

(iii) Arthritis Foundation? ❑ Yes ❑ No

(iv) An advisory committee set up by a pharmaceutical company?

❑ Yes ❑ No

If yes, please circle one of the following:

Companies sponsoring Enbrel/Remicade/Humira OR Other companies

(v) Pharmaceutical company employee?

❑ Yes ❑ No

Please indicate company name……………………………………
………………………………………………………………………

(vi) Other committee or organisation with a substantial
influence on the PBS restrictions? ❑ Yes ❑ No

If yes, please name…………………………………………………….
………………………………………………………………………

Thank you for your time and effort in completing this questionnaire.

Please return to Christine Lu Therapeutics Centre, St Vincent's Hospital & The University of New South Wales

PLEASE NOTE:

The questionnaire will contain an additional page for RHEUMATOLOGISTS (as page 3), or an additional page for PATIENTS (as page 3).
For other participants, the questionnaire distributed will contain only the FIRST and the SECOND pages.

Additional page for RHEUMATOLOGISTS

RHEUMATOLOGISTS, please also complete this page.

The following questions relate to your experiences with the prescription of TNF inhibitors

Please tick one box indicating the number of years practicing as a rheumatologist:

- ❑ less than 2 years
- ❑ 3-9
- ❑ 10-20
- ❑ more than 20

Please indicate:

Number of patients on subsidized etanercept (Enbrel) treatment   ………….

Number of patients on subsidized infliximab (Remicade) treatment   ………….

Number of patients on subsidized adalimumab (Humira) treatment   ………….

Thank you for your time and effort in completing this questionnaire.

Please return to Christine Lu
Therapeutics Centre, St Vincent's Hospital & The University of New South Wales

Additional page for PATIENTS

PATIENTS, please also complete this page.

The following questions relate to your experiences with the prescription of Enbrel, Remicade, or Humira (etanercept, infliximab, or adalimumab)

Please tick box(s) relevant to your status

❑ I am currently receiving Enbrel / Remicade / Humira (*Please circle one*)

❑ I am currently NOT taking any one of these medicines, but have considered taking one of these medicines

❑ I am applying to start one of these medicines.

❑ My treatment with Enbrel/Remicade/Humira is **subsidized by the PBS**

❑ I have taken one of these medicines previously as private prescription

❑ I have been granted approval to continue Enbrel/Remicade/Humira therapy after initial 16 weeks of treatment

❑ Treatment with Enbrel/Remicade/Humira was discontinued due to side effect(s)

❑ Subsidized treatment with Enbrel/Remicade/Humira was discontinued due to disapproval of application for continuation of therapy

❑ I am currently working full-time / part-time / not working (*Please circle one*)

❑ Other medical conditions:
If yes, please name……………………………………………………….
……………………………………………………………………………………

Thank you for your time and effort in completing this questionnaire.

Please return to Christine Lu
Therapeutics Centre, St Vincent's Hospital & The University of New South Wales

Appendix 3.6

Study description and patient selection criteria

Research study: Exploring stakeholders' perceptions of subsidized access to tumour necrosis factor (TNF-alpha) inhibitors in Australia

Chief Investigator: Prof Ric Day
Co-Researchers: Christine Lu

Study Description
Access to effective medicines is becoming increasingly problematic with increasing consumer expectations and resource constraints as the cost of healthcare continues to rise. Restricted access arrangements have been established on the Pharmaceutical Benefits Scheme (PBS) to subsidize 'high-cost' drugs. The PBS subsidizes the cost of the new biologic agents, tumour necrosis factor (TNF-alpha) inhibitors: etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira), for the treatment of rheumatoid arthritis (RA), but only for a subset of individuals. Those that are granted subsidized access to these drugs under the PBS must satisfy strict eligibility criteria, and their clinical outcomes are assessed, with continuation of therapy after 3 months only approved if predetermined response criteria are met. Patients must sign a form to acknowledge and agree with this continuation restriction. Interviews will be conducted, as part of the PhD research programme, to qualitatively document stakeholders' perceptions of restricted, subsidized access via the PBS to these three medicines.

Aim of the study
The aim of this project is to explore stakeholders' experiences, concerns, and perceptions of the collaboration process, and the arrangements of subsidized access to the TNF inhibitors via the PBS for the treatment of RA, and possible improvement of this access.

Patient Inclusion Criteria
Patients will be included if:
1) Patients are18+ years old
2) Patients with rheumatoid arthritis
3) The patient is taking etanercept, infliximab, or adalimumab
4) The patient has taken etanercept, infliximab, or adalimumab previously
5) Treatment with etanercept, infliximab, or adalimumab have been considered for the patient or an application to initiate treatment is in the review process by the Health Insurance Commission
6) Patients speak fluent English
7) Patients are able and willing to given consent

Study procedures
Potential participants can contact the study co-ordinator (Christine Lu) for more information, and/or indicate their interest in participating. Appropriate location and time for interview will then be arranged. A Participant Information Sheet and a Consent Form will be sent out and to be returned to CL.

For further information, please contact:
Christine Lu (02) 83822199, email: christine.lu@student.unsw.edu.au
Prof Ric Day (02) 83822331. email: r.day@unsw.edu.au

Appendix 3.7

Interview guide

Access to high-cost drugs in Australia via the Pharmaceutical Benefits Scheme – Case study: Tumour necrosis factor inhibitors

Introduction
Background to study, purpose of research, what happens during/after interview

Discussion topics

PBS arrangements for access
Initiation criteria: Methotrexate, combination of 3 DMARDs, leflunomide, cyclosporin, rheumatoid factor +ve, severe active RA)
Patient agreement process
Continuing criteria: 50% improvement in joint count, reduced ESR and/or CRP levels
Limited prescribing rights
Risk sharing
Application process

Collaboration between the different stakeholder groups
Pre-listing
Post-listing

Educational material / activities / services
To patients
To rheumatologists
? To GPs
Contact/services through GPs, nurses
Main source of information
Feedback

Interview guide

1. The arrangements of access to the TNF inhibitors

a. Where did you first hear about the arrangements of access to TNF inhibitors via the PBS?
b. What prompted you to begin using these drugs?
c. Was your decision to prescribe these drugs influenced by anything or anyone in particular (for example, colleagues, literature – safety/efficacy, advertising, representatives, meetings, patients, arrangements – paperwork, risk-sharing between government and Wyeth for etanercept)?
d. What other sources of information did you use before prescribing the drug, or during the course of the treatment?
e. What do you see as the primary objective of the PBS arrangements of access?
f. What do you see as the particular value of the PBS arrangements of access?
g. What about any concerns you might have?
h. Are you aware of the approximate cost of the medicine paid by the PBS per month (ie one script)?

i. How important do you think the arrangements of access to TNF inhibitors have improved management of rheumatoid arthritis?

2. Collaboration (pre-listing)

j. Have you been involved in the consultation process in regards to developing restrictions or arrangements to access the TNF inhibitors via the PBS?
    a. Can you briefly describe your role in the consultation process?
    b. Who else took part in the consultation process?
k. How confident or appropriate do you feel about the representation of the groups participated in the collaboration process?
l. Who do you think should take part in the consultation process for formulating the arrangements or restrictions for access?

2b. Collaboration (post-listing)

m. What is the extent of your contact with other rheumatologists, local general practitioners, HIC administrators, consumer organization, the PBAC?
    a. What were the purposes of these contacts?
n. What do you see as the role and responsibility of the prescribers? The PBAC? The industry? Arthritis Foundation?
(Regarding collaboration pre-listing & post-listing. For example, education, service provision etc)

3. Education
o. Who, in your view, has responsibility in informing/'educating' the prescribers (and the public) regarding PBS restriction changes, or new complex PBS restrictions?

Final questions
p. How important an advance do you think the consultation approach and access arrangements represent?
q. If a new and expensive drug comes along that is a significant advance for the treatment of a chronic disease, what differences would you like to see in the process of getting it listed and using it?

Appendix 4.1

Data Request to Health Insurance Commission, Commonwealth

Department of Health and Ageing

State Manager Tasmania
Health Insurance Commission
242 Liverpool Street
Hobart
TAS 7000
02 July 2004

RE: Usage of etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®) for the treatment of Rheumatoid arthritis – Proposal for Research Collaboration

Dear Manager,

Access to expensive but innovative medicines is a major problem for healthcare systems and individuals. Australia's Pharmaceutical Benefits Scheme (PBS) has established a restricted access scheme to a class of effective but expensive biologic agents, etanercept, infliximab and adalimumab for a targeted subgroup of patients with severe rheumatoid arthritis to ensure 'cost-effectiveness' and to promote predictability in volumes of use and thus costs. The arrangements for access involved a number of interesting features: strict initiation criteria, eligibility for continuation of therapy managed via objective outcome measurements, and a 'patient agreement' process to ensure understanding and acknowledgement from patients.

The process of establishing access arrangements to these drugs as well as the resultant access mechanism is of considerable importance and interest internationally as well as to the Australian public and profession. As part of a PhD research program that aims to provide further understanding on the question of supplying useful but expensive drugs when budgets are tight and 'cost effectiveness' is limited to a 'severely affected' sub-set of patients, together with our postgraduate student, Christine Lu (enrolled in The University of New South Wales), we would like to examine this experiment from multiple perspectives, including a study on the PBS usage and expenditure information of the above three drugs over a period of 24 months (August 2003 to August 2005).

Please find attached our study proposal providing more specific details of the data and information we would like to study. Data will be analysed, grouped, and discussed. The purpose is to examine the 'experience' with this set of arrangements for access to TNF inhibitors, and to note the changes and their effect on the 'experience' going forward with a view to commenting on the strengths and weaknesses and possible improvements for the future.

We have an excellent group of advisors and collaborators for this research – we would like to add relevant and interested people from HIC to be investigators also and to offer our interest and time in helping analyse the experience with this access 'experiment'. We would wish to plan publications with HIC personnel as co-authors. Thus, the planning of analyses and presentations should be collaborative if this is of interest to you and acceptable. We do hope this will be helpful and of interest.

We understand that we are requesting a large amount of information, and we are prepared to for Christine to do this time-consuming collection of data and information. Your collaboration will be greatly appreciated and we thank you in anticipation for considering this request. We look forward to your confirmation as to which data and information will be likely to be available to us for this research program.

Thank you for your kind consideration.

Yours sincerely,

Ric Day

Supervisor/Chief Investigator

P.S. Supporting letters will be coming from Prof Lloyd Sansom (Chair of PBAC), and Prof Andrea Mant (Chair of DUSC).

Full research program title
An examination of systems of access to important high-cost drugs: a critical analysis of the nationally subsidized scheme of access of patients to tumour necrosis factor (TNF-alpha) inhibitors in Australia.

Background
Access to new, effective medicines is becoming increasingly problematic internationally. Payers in health care systems, including Australia's national pharmaceutical subsidy programme, the Pharmaceutical Benefits Scheme (PBS), face challenges of how to best spend resources while dealing with increasing consumer expectations and substantive resource constraints as the cost of healthcare continues to rise. Debates centre on which treatments should be provided, which patients should receive priority and under what criteria, and who should be involved in the decision-making process. These decisions are of high importance since insufficient access can lead to poor quality of care and health outcomes, and inadequate treatment may result in major costs. Appropriate access to medicines is further complicated by the uncertainty of the long-term safety and high cost of the majority of these medicines.

The PBS has established a set of arrangements to access high-cost medicines (HCMs) in an attempt to balance these forces and maintain the viability of the PBS. Representative of these type of arrangements, but in many ways novel, are those now in place for the new class of biologic agents, tumour necrosis factor (TNF-alpha) inhibitors for the treatment of rheumatoid arthritis (RA). The process that led to the access to etanercept (the first TNF inhibitor to be listed on the PBS) via the PBS was based on a unique collaboration between the respective stakeholders: the Pharmaceutical Benefits Advisory Committee (PBAC), the Sponsor, specialist rheumatologists and consumer representatives (Arthritis Foundation of Australia).

The TNF inhibitors that are subsidized under the PBS are etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira). The PBS subsidizes the cost of these drugs but only for a subset of individuals where 'cost-effectiveness' has been demonstrated. Those that are granted subsidized access to these drugs under the PBS must satisfy strict eligibility criteria, and their clinical outcomes are assessed, with continuation of therapy after three months only approved if predetermined response criteria are met. Patients must sign a form to acknowledge and agree with this restriction to ongoing subsidisation. Prescribing rights are limited to specialists with expertise in the management of RA.[1]

There are limited published studies examining consultation processes to reach consensus on arrangements of access to HCMs in Australia, arrangements to access HCMs operated via national subsidy systems, or the critical linkage between subsidized access to HCMs and the quality use of HCMs in Australia or internationally. The aim of this PhD research programme is to examine the collaboration between stakeholders, and the access to HCMs via the PBS, using as a case study the TNF inhibitors experience. We also wish to assess the extent to which the access mechanism is consistent with Australia's National Medicines Policy,[2] the overall aim of which is to ensure that optimal health outcomes and economic objectives are achieved for individuals and the community in Australia. The findings from this research programme will provide a foundation and guide to future implementation of the evolving systems of subsidised access to HCMs in Australia and elsewhere.

Reference:
1. Commonwealth Department of Health and Ageing. Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners, February 2004. Commonwealth of Australia, Canberra.
2. National Medicines Policy 2000, Commonwealth Department of Health and Ageing, Australia.

Hypothesis of this research programme:

"The arrangements for access to TNF-alpha inhibitors via the PBS are consistent with Australia's National Medicines Policy."

The National Medicines Policy includes four objectives:
1. Timely access to the medicines that Australians need, at a cost individuals and the community can afford
2. Medicines meet appropriate standards of quality, safety and efficacy
3. The quality use of medicines (QUM)
   a. judicious selection of management options
   b. appropriate choice of medicines
   c. safe and effective use
4. Maintaining a responsible and viable medicines industry in Australia

The arrangements for access to TNF inhibitors involve:
(i) Collaborative approach pre-listing between the PBAC, ARA, and the sponsor in establishing the arrangement of access to these drugs via the PBS, and
(ii) Resultant access arrangements of the TNF inhibitors, which include:
(a) Initiating criteria (trials and inadequate response with methotrexate, combination of disease-modifying anti-rheumatic drugs, leflunomide, cyclosporin, rheumatoid factor positive status, and severe active rheumatoid arthritis)
(b) Patient agreement process
(c) Continuation criteria (including a 50% improvement in joint count) at three months
(d) Limited prescribing rights

Purpose of Request
The aims of this study are to evaluate the impact of implementing the PBS arrangements for access to etanercept, infliximab, and adalimumab, and to examine the implementation of the restricted access mechanism at a number of levels, the compliance of prescribers to the restrictions, and the pattern of use of these drugs.
The information will be used in combination with findings from the qualitative phase of the study to develop and propose interventions to appropriately and optimally access HCMs via a nationally subsidized system.

Details of Research Team at UNSW and St Vincent's Hospital Sydney

Investigators
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Individuals who have generously provided their advice on the project (to date):
Prof Lloyd Sansom
A/Prof Lyn March
Dr Jim Bertouch
A/Prof Andrea Mant
Dr Sallie Pearson

Proposed time period of the data required for the project
01 August 2003 to 31 December 2005 (30 months)

The PhD program is to be completed by August 2006. Data collection is to be completed by
Mid January 2006 to allow sufficient time for analysis and completion of thesis.

General Data Requirement
Information is requested on the number of applications, number of approvals, continuations,
and reimbursement for etanercept, infliximab, and adalimumab therapies.
Information and reports are requested on audit of utilization of etanercept, infliximab, and
adalimumab via the PBS.

Format of data requested (that can be accessed, prepared and analysed Ms Lu with
attention to confidentiality as required)
Excel spreadsheet
Written reports

Data delivery preferred (Travel of Ms Lu to HIC will be acceptable if this is optimal from HIC
perspective)
Requested data would preferably be made available in both CD format and hardcopies.

Contact for Request
Christine Lu
02 8382 2199

Exact Data Requirements

PBS item numbers:
8637N Etanercept (initial therapy, adult rheumatoid arthritis)
8638P Etanercept (continuation therapy, adult rheumatoid arthritis)
6397Q Infliximab
8741C Adalimumab (initial therapy)
8737W Adalimumab (continuation therapy)

For each drug (etanercept, infliximab, and adalimumab), the following data are requested:
Number of initiating treatment applications received (per month)
Number of initiating treatment applications approved (per month)
Number of continuing treatment applications received (per month)
Number of continuing treatment applications approved (per month)
Common issues of enquiries (top 20 issues)

If possible this data would be provided grouped into 3 geographical categories:
1= Capital city, other metro
2= Large rural, small rural, other rural, and
3= Remote center, other remote, and unknown

Further detailed data and information Request

For the initiating treatment applications received, demographics and medication history of the de-identified (represented by initials or numbers), individual applicants are requested for further analysis, and the application status (whether application was approved, reasons if not approved) is also requested.

Details requested for inclusion:
Patient's date of birth
Previously on this medication: Y/N
The dosage of methotrexate tried but associated with an inadequate response, and the duration of treatment
Intolerant to treatment with methotrexate 20mg per week, or contra-indicated, with details of contra-indication or intolerance.
Reasons given if methotrexate dose was lower than 20mg per week
The names of other disease-modifying anti-rheumatic drugs (DMARDs) tried in combination with methotrexate
Details of contra-indication or intolerance to methotrexate.
Failure to respond to which of the following: leflunomide, leflunomide with methotrexate, or cyclosporine?
ESR and CRP levels, and reasons elevated ESR or CRP criteria could not be met.
Total joint count
Any additional contacts between the HIC and the prescriber with regard to the application; details/issues of these contacts
Date of application
Date of decision regarding application

For the continuing treatment applications received, details of clinical and laboratory assessments of the de-identified (represented by initials or numbers), individual applicants are requested for further analysis, and the application status (whether continuation of therapy was approved, reasons if not approved) are requested.

Detailed requested include:
ESR or CRP levels
Baseline levels of ESR and/or CRP
Recent total joint count
Baseline joint count
Any additional contacts between the HIC and the prescriber with regard to the application, details/issues of these contacts
Date of application
Date of decision for application

Client Liaison Officer
Client Liaison Unit
Information Strategy Section
Information Services Branch

Dear Sir/Madam,

Thank you for considering our request for HIC information with Request ID: 2004/CO07182.

We would like to request opportunities to conduct interviews with staff at the Health Insurance Commission who have been involved in reviewing authority applications for subsidisation of etanercept, infliximab, and adalimumab. The aim of the interviews is to explore their opinions and experience with the reviewing process. Statistical data is not a part of this request. Please find the additional information as requested below.

We look forward to hearing from you. Please don't hesitate to contact us if further information is required.

Kind regards

Christine Lu

Christine Yi-Ju Lu
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BPharm MSc(Biopharmaceuticals)
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Requestor Details
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Other Investigators – Details
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First Name   : Kenneth M
Surname   : Williams
Occupation   : Deputy Director of Department of Clinical Pharmacology and
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The HIC is committed to improving Australia's health through the provision
of information to health consumers.

1.   How does the information you are requesting contribute to improving
Australia's health?

Appropriate and affordable access to medicines of acceptable quality, safety, and efficacy,
and using medicines rationally save lives and improve health outcomes for consumers.
However, access to medicines is complicated by resource constraints, high cost of the
majority of the innovative agents, and limited data of their long term safety. As a part of a
PhD research program focusing on the access to high-cost medicines via the
Pharmaceutical Benefits Scheme, we would like to explore stakeholders' perceptions on the
arrangements for access to the group of biological agents – tumour necrosis factor inhibitors
(etanercept, adalimumab, and infliximab). Stakeholders we would like to conduct interviews
with include managers and administrators at the HIC who have been involved in reviewing
the applications for PBS reimbursement for these medicines. The information requested will
contribute to a better understanding of the access to these medicines and we hope that the
findings may be used to enhance appropriate access to these medicines.

2.   Are you requesting this information on behalf of someone else?
     No

3.   Will this information be published/presented? Yes

     If yes, in what forum/publication?

The results of this study forms part of a PhD thesis, and will be presented at conferences, as
well as submitted to peer-reviewed journals for consideration of publication.

4. From which program(s) do you require data?

   Medicare /PBS /DVA* / Enrolment /PIP / Immunisation
   * Requires permission form the Department of Veterans' Affairs
   (Please delete unwanted)

PBS.
In addition, we would like to request opportunities to interview the staff at the HIC who were involved in reviewing the authority application in regarding to the medicines mentioned above.

5. Please list all MBS / PBS item numbers, or item groups required.

8637N Etanercept (initial therapy, adult rheumatoid arthritis)
8638P Etanercept (continuation therapy, adult rheumatoid arthritis)
6397Q Infliximab
8741C Adalimumab (initial therapy)
8737W Adalimumab (continuation therapy)

6. At what summary level do you require this data:

N/A

   National / State / Local Government Area (LGA) / Statistical Local
   Area (SLA) or Division of General Practice (DGP)
   (Please delete unwanted)

   Is this based on patient or provider location?
   Patient / Provider
   (Please delete unwanted)

7. Which date period is required?

N/A
   From ..../..../.... To ..../..../....

   Is this based on: Medicare: Date of Service (DOS),
                Date of Processing (DOP)
                DOS / DOP
                (Please delete unwanted)

                PBS: Date of Supply (DOS), Date of Prescribing
                (DOP),
                Date of Claim (DOC)
                DOS / DOP / DOC
                (Please delete unwanted)

Appendix 5.1

DUSC Data Request – Utilisation of anti-rheumatic biological medicines

Data request – Utilisation of drugs for rheumatoid arthritis in Australia

Request 1. From the DUSC Database

Data extracted by the PBS/RPBS item numbers, the generic name of the drug (please include the ATC codes), and the cost reimbursed by PBS/RPBS.

The output should include the PBS item numbers, ATC code, expenditure, and the generic name of the all the drugs as listed below:

Biological agents for the treatment of rheumatoid arthritis: etanercept, adalimumab, infliximab, and anakinra.

The PBS items codes of interest are attached at the end of this request form.

We would like the data separated into the following:
PBS (subsidised and on the PBS)
RPBS (subsidised and on the RPBS)
Under co-payment (PBS listed but not subsidised: note the increase in co-payment may have an impact on this data)
Private

In the output, please report the Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005

Request 2. From the Age and Gender Summary File for the HIC transaction database (date of supply data)

Data extracted and listed by Item code (as above): as listed on the DUSC map

Data provided is for R/PBS only.

In the output report the number of prescriptions by 5 year age group and gender.
Report period from the start of the age/gender summary file. Report the data by month starting at January 2000 until July 2005 (we understand that data is more accurately captured since May 2002).

Extract data by PBS/RPBS item numbers (including ATC codes) and generic drug name.
The PBS items codes of interest are in the attached at the end of this request.

The output should include ATC codes, drug generic name and item numbers.

We would like the data separated into the following:
PBS (subsidised and on the PBS)
RPBS (subsidised and on the RPBS)
Under co-payment (PBS listed but not subsidised: note the increase in co-payment may have an impact on this data)
Private

In the output, please report the Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005

Request 3. R/PBS Data Stratified by Provider Location (RRMA Classification)

Extract data by PBS/RPBS item numbers (including ATC codes) and generic drug name.
The PBS items codes of interest are in the attached at the end of this request.

Please stratify the above by division of practice codes. Please stratify prescribers: general practitioners, or specialists (if possible, stratify into rheumatologists or clinical immunologists). Please stratify the above by postcodes of prescribers (using major practice postcode of provider in date of prescribing summary file). Map this postcode onto division of practice postcodes.

In the output, please report Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005.

Request 4. R/PBS Data Stratified by State

Extract data by PBS/RPBS item numbers (including ATC codes) and generic drug name.
The PBS items codes of interest are in the attached at the end of this request.

Stratify the above by Australian State or Territory.

In the output, please report Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005.

Request 5. Number of patients on biological agents

Number of patients commenced on etanercept, infliximab, adalimumab, and anakinra (as close approximation as possible).
Number of patients continued on etanercept, infliximab, adalimumab, and anakinra (as close approximation as possible).
Number of patients switched on etanercept, infliximab, adalimumab, and anakinra (as close approximation as possible).

Please stratify the above by Australian State or Territory, on a monthly basis (where possible). Reporting Period: Jan 2000 – July 2005.

Rheumatoid arthritis drugs PBS item numbers

PBS item number	Generic Name of Drug & Strength
8637N	Etanercept 25mg
8638P	Etanercept 25mg
6397Q	Infliximab
8737W	Adalimumab 40mg
8741C	Adalimumab 40mg
8773R	Anakinra 100mg
8774T	Anakinra 100mg

Appendix 6.1

DUSC Data Request – Utilisation of conventional disease-modifying

anti-rheumatic drugs

Data request – Utilisation of drugs for rheumatoid arthritis in Australia

Request 1. From the DUSC Database

Data extracted by the PBS/RPBS item numbers, the generic name of the drug (please include the ATC codes), and the cost reimbursed by PBS/RPBS.

The output should include the PBS item numbers, ATC code, expenditure, and the generic name of the all the drugs as listed below:

Disease-modifying anti-rheumatic drugs: gold preparations, hydroxychloroquine, penicillamine, leflunomide, and methotrexate.

The PBS items codes of interest are attached at the end of this request form.

We would like the data separated into the following:
PBS (subsidised and on the PBS)
RPBS (subsidised and on the RPBS)
Under co-payment (PBS listed but not subsidised: note the increase in co-payment may have an impact on this data)
Private

In the output, please report the Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005

Request 2. From the Age and Gender Summary File for the HIC transaction database (date of supply data)

Data extracted and listed by Item code (as above): as listed on the DUSC map

Data provided is for R/PBS only.

In the output report the number of prescriptions by 5 year age group and gender.
Report period from the start of the age/gender summary file. Report the data by month starting at January 2000 until July 2005 (we understand that data is more accurately captured since May 2002).

Extract data by PBS/RPBS item numbers (including ATC codes) and generic drug name. The PBS items codes of interest are in the attached at the end of this request.

The output should include ATC codes, drug generic name and item numbers.

We would like the data separated into the following:
PBS (subsidised and on the PBS)
RPBS (subsidised and on the RPBS)
Under co-payment (PBS listed but not subsidised: note the increase in co-payment may have an impact on this data)
Private

In the output, please report the Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005

Request 3. R/PBS Data Stratified by Provider Location (RRMA Classification)

Extract data by PBS/RPBS item numbers (including ATC codes) and generic drug name.
The PBS items codes of interest are in the attached at the end of this request.

Please stratify the above by division of practice codes. Please stratify prescribers: general practitioners, or specialists (if possible, stratify into rheumatologists or clinical immunologists). Please stratify the above by postcodes of prescribers (using major practice postcode of provider in date of prescribing summary file). Map this postcode onto division of practice postcodes.

In the output, please report Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005.

Request 4. R/PBS Data Stratified by State

Extract data by PBS/RPBS item numbers (including ATC codes) and generic drug name.
The PBS items codes of interest are in the attached at the end of this request.

Stratify the above by Australian State or Territory.

In the output, please report Prescriptions per month per year and DDD/1000pop/day per month (where possible).
Reporting Period: Jan 2000 – July 2005.

Rheumatoid arthritis drugs PBS item numbers

PBS item number	Generic Name of Drug & Strength
1095P	Auranofin
2016D	Sodium Aurothiomalate 10mg
2017E	Sodium Aurothiomalate 20mg
2018F	Sodium Aurothiomalate
2721F	Penicillamine 125mg
2838J	Penicillamine 250mg
1512N	Hydroxychloroquine
1622J	Methotrexate 2.5mg
1623K	Methotrexate 10mg
2396D	Methotrexate 5mg/2mL
2688L	Azathioprine 25mg
2687K	Azathioprine 50mg
1266P	Cyclophosphamide 50mg
1079T	Cyclophosphamide 500mg
1080W	Cyclophosphamide 1g
1031G	Cyclophosphamide 2g
2093E	Sulfasalazine 500mg
2096H	Sulfasalazine 500mg enteric coated
8657P	Cyclosporin 10mg
8658Q	Cyclosporin 25mg
8659R	Cyclosporin 50mg
8660T	Cyclosporin 100mg
8661W	Cyclosporin Oral liquid
6109M	Cyclosporin 50mg IV solution
6110N	Cyclosporin 250mg IV solution
6232B	Cyclosporin 10mg
6352H	Cyclosporin 25mg
6353J	Cyclosporin 50mg
6354K	Cyclosporin 100mg
6125J	Cyclosporin Oral liquid
8373Q	Leflunomide starter pack
8374R	Leflunomide 10mg
8375T	Leflunomide 20mg