Compliance to Medicines Working Group (CMWG)

Report

To

Pharmaceutical Benefits Advisory Committee (PBAC)

(April 2010)

Table of Contents

Executive Summary

The Pharmaceutical Benefits Scheme (PBS) subsidises medicines that improve health outcomes and provide value for money. Compliance with medication regimens is one factor that can influence the achievement of health outcomes and affect the cost-effectiveness of a medicine. Therefore, evaluating evidence on the extent of compliance to medicines and the effect on health outcomes is of concern to the Pharmaceutical Benefits Advisory Committee (PBAC) when considering therapies to be recommended for subsidy.

Evaluation of consumer compliance has also become increasingly important to the PBAC since the amendment of the *National Health Act* associated with the Pharmaceutical Benefits Scheme (PBS) Reforms in 2007. These statutory changes now include a provision Subsection 101(4AC) that requires the PBAC to evaluate claims of improved compliance to combination items and advise the Minister when a combination item significantly improves compliance.

While the above amendments to the *Act* pertains specifically to combination items, the CMWG, at its initial meeting, decided that this report should include information on measuring compliance and the effects of compliance on health outcomes for all types of medicines. The intent was to provide the PBAC with information on measuring and assessing the effects of compliance on health outcomes attributable to the use of different formulations such as extended release and depot products. The CMWG was also concerned that the complexity of assessing compliance to medicines was reflected in the report.

Part A: Definitions, Perspectives and Factors Influencing Compliance to Medicines

In this report, the term *compliance* has been used broadly to encompass all aspects of consumers' acceptance of, adherence to and persistence with a prescribed medicine regimen. The following definitions were accepted by the CMWG:

Acceptance: The consumer's informed decision to undertake behaviours that are expected to lead to improved health outcome. In this report, medicine taking is assumed to be part of the agreed regimen. (WHO, 2003)

Adherence: The extent to which the consumer conforms to the agreed behaviours, with respect to timing, dosage and frequency of medication taking. (Cramer, 2007)

Persistence: The duration of time from initiation to discontinuation of therapy. (Cramer, 2007)

An understanding of the context in which a medicine is prescribed and taken is fundamental when evaluating interventions to improve compliance. It is also important to consider compliance from the perspectives of the consumer, the health professional and the payer (for PBS medicines the payer refers to the Commonwealth Government). The priorities of consumers, prescribers and payers may differ: the appropriate level of compliance for an individual may not be the same as the prescriber's view of the 'optimum level' of compliance or the population level of compliance that is considered appropriate by a payer.

Health benefits from improved compliance are often assumed rather than demonstrated in health technology assessments. In some instances, compliance to therapy has been shown to be positively associated with improved health outcomes, but methodological difficulties and

lack of data have impeded broader studies of relationships between compliance and health outcomes. Limitations of observational methods used in much of the current compliance research cause difficulties in establishing whether a particular intervention such as the use of a combination product improves compliance in a way that ultimately improves health outcomes.

Statistical differences in measured levels of compliance, based on counts of prescription refills, do not necessarily translate into clinically meaningful differences in health outcomes. The compliance literature often suggests that a compliance level of at least 80% is necessary, but little evidence exists to support this assertion in many settings. Protease inhibitor therapy in HIV provides a rare example where there is evidence that a high level of adherence is required for an adequate therapeutic effect.

Improvements in compliance require multidisciplinary and multilevel interventions that address individual consumers' varying experiences. Many diverse factors may influence a consumer's decision to take a medicine. Some of these factors are related to the medicines themselves and the types of formulations. These factors affect different consumers to differing degrees, both within and between populations. Understanding the effects of such modifying factors within the relevant population is critical to the interpretation of research assessing the effects of interventions to improve compliance.

Part B Measuring and Assessing Compliance

Compliance to medicines is difficult to measure, particularly compliance with long-term self-administered therapies. A variety of methods can be used to measure compliance. These methods often produce results that correlate, but they do not always produce the same estimate, even when applied to the same data. Variability in the application of methods to measure compliance also limits comparability of results from different studies of compliance to the same medicine or different formulations of medicines.

The CMWG identified the advantages and disadvantages of the many different study designs and methods used to study compliance. The study design and methods should be tailored to the compliance question. The usual hierarchy of evidence for studies of efficacy and safety may not necessarily apply to studies of consumer compliance. Ideally, studies should be designed to measure both compliance and health outcomes, use multiple measures of compliance (such as adherence and persistence) and include self-reported measures of compliance.

Randomised controlled trials (RCTs) have a role in assessing the effect on health outcomes of interventions to improve compliance, but they have limitations when used to assess compliance to medicines in consumers with long-term chronic conditions. More use could be made of pragmatic randomised trials in measuring compliance under conditions of routine clinical use. Such studies could involve randomising consumers to different medicines at the prescriber level and assessing compliance via PBS prescription refill data. This approach would minimise the cost of the research and the effects of participant (and possibly selection) effects.

The analysis of administrative data (including data on prescription refills) is increasingly used to assess consumer compliance. Prescription refills have become a common surrogate for medication consumption and are often used as indicators of adherence or persistence. The

major limitation of all such observational studies is that, because subjects are not randomised, considerable potential exists for bias due to unknown confounders. Consequently, observed differences in compliance or health outcomes cannot necessarily be attributed to the intervention of interest. However, the use of observational designs in studies of compliance is a developing research area, and study designs and analytical methods are evolving.

Retrospective observational studies of administrative data can be useful in measuring compliance to broad classes of drugs, and are better suited to research questions on persistence and switching between medicines. They may address adherence where dosage is known and research designs can account for gaps in treatment, but they cannot be used to assess acceptance of medicines unless prescription refill data can be linked to prescriber data.

Administrative data provide a relatively inexpensive way of assessing compliance in large numbers of consumers, thereby increasing statistical power. Nonetheless caution is required in interpreting their findings, because statistically significant changes in medication possession do not necessarily translate into clinically meaningful improvements in health outcomes. It is important to analyse all data at the de-identified individual consumer level, and to report the distribution of compliance rather than the proportions of consumers within arbitrary compliance ranges (e.g. a medication possession ratio (MPR) of 80% or more). Understanding the underlying pattern of compliance in a population and the effect of any intervention on compliance is critical in understanding the likely effect of an intervention (such as an alternative product formulation) on health outcomes.

The measurement of compliance from prescription refill data has been developed largely in the USA and other countries where administrative datasets link prescriber and health service utilisation data. In Australia, similar studies of compliance and its effects on health outcomes are limited by the absence of data on medicine doses, number of days of supply and treatment indication in PBS and Repatriation PBS (RPBS) datasets. There is also limited ability to link PBS data with other health service data. Thus studies based on Australian data have little scope to adjust or control for confounding in observational studies of compliance. Improved access to PBS data that can be linked to other health datasets would greatly assist in this area of research.

The current lack of comprehensive linked health data poses major challenges for those making decisions about the provision of health services in Australia. Observational studies of compliance in different populations around the world are unlikely to be directly transferable to the Australian setting. In the absence of Australian evidence, overseas studies should be interpreted in the light of known differences between Australian and other countries' populations and health service settings.

Measuring the Effects of Compliance on Health Outcomes

An association between compliance and an intervention must be shown before any effect on clinical outcomes can be attributed to the intervention. Ideally the study should include measures that directly link compliance and health outcomes. This will give decision makers the strongest evidence on whether or not improvements in compliance translate into better health outcomes in the population treated.

Where such direct evidence is not available, it may be possible to establish a relationship between improved compliance and an intermediate health outcome (e.g blood pressure) that

predicts better definitive health outcomes (e.g. the occurrence of stroke). For combination therapies, it may be possible to use evidence on the efficacy of the individual components to estimate the effects of the combined product over time. A similar approach could also be used with long-acting formulations where the effects of the short-acting therapy on health outcomes are known. Such approaches depend on modelling, and do not substitute for collecting more direct evidence where possible. If direct evidence cannot be obtained, modelling does provide a systematic estimation of the potential benefits, using assumptions derived from the best available evidence.

Measuring the cost effectiveness of interventions to improve compliance

In order for a compliance-enhancing intervention (such as a change in medicines or formulation) to be cost effective, an economic evaluation should demonstrate that:

- The intervention improves compliance in a way that can be linked to a health gain;
- The cost of the intervention (i.e. the alternative or substituted medicine) must be such that it is cost-effective.

Although not specifically relevant to s101(4AC), the integration of compliance to different formulations in pharmaco-economic evaluations is a major challenge and the results to date have been less than clear. Changes in compliance affect both the numerator and the denominator of the incremental cost-effectiveness ratio (ICER), so the effect of compliance on an ICER is not always predictable. The cost-effectiveness of interventions to improve compliance is also affected by factors which vary over time: for example varying states of consumer compliance and changes in the costs of new formulations and comparators.

Part C: Comparing compliance with combination items versus alternative therapies

The following framework poses important questions from a funder perspective in evaluating evidence to support claims of increased compliance to combination items.

Framework for assessing evidence to support claims of increased compliance to combination items.

Question	Potential sources of evidence	Reference to this Report
1. What is currently known about the level of compliance to this medicine(s)? • Considering acceptance, adherence and persistence?	Structured literature review, systematic review. Current persistence in PBS administrative data and prescription claims data. Other studies of compliance, including validated self report, direct observation, pill counts, prescription refills, electronic medicine monitoring.	Part B
2. What is known about factors that affect compliance to this medicine? • Individual consumer behaviours and caregiver behaviours. • Disease characteristics. • Characteristics of the practitioner or prescriber. • Health system factors. • Characteristics of the medicine, the formulation and the regimen. Consider the extent to which each factor may contribute to non-compliance (e.g. consumer factors 10%, system factors 10%, medicine formulation factors 50%)	Identify potential factors that could affect the use of this medicine. • Qualitative and quantitative studies of factors affecting compliance. • Cross-sectional surveys of reasons for non-compliance. • Self report surveys in RCTs including reasons for non-compliance.	Part A.3
3. How, and to what extent, can the combination item affect the factors contributing to non-compliance in the population of interest?	• Published studies • Plausible explanation • Survey of prescribers • Survey of consumers	Part A
4. Is there evidence available to show that there are measured differences in compliance and, if so, that these are associated with use of the combination item versus its alternative therapies?	Comparative studies of compliance to the combination item versus alternative therapies e.g. retrospective studies or pragmatic trials.	Parts B.2 and B.3
5. Is any measured difference in compliance sufficient to affect health outcomes, i.e. is it clinically significant? How critical is compliance to achieving the desired health outcomes for the medicine prescribed?	Studies of the effect of compliance on health outcomes (preferably from studies designed to measure compliance that also include measures of health outcomes). • Pharmacokinetic studies. • Dose-response studies including data on duration of medicine usage. • Outcomes data from RCTs.	Part B.5
6. What is the effect on PBS expenditure of retaining the price of the combination item when the price(s) of its component medicine(s) undergo a statutory price reduction, in comparison with applying these price reductions to the combination item?	• Estimate of projected PBS utilisation at current listed price • Estimate of projected PBS utilisation following price reductions applied from component medicines	Part C.5

Comparative studies of combination items and the component medicines taken concomitantly

The compliance literature has not yet extensively compared rates of compliance between consumers prescribed combination items and those prescribed the component medicines

taken concomitantly. No consensus exists among pharmaco-epidemiologists on how to conceptualise and measure the effects of these products on compliance.

The issues listed below arise when prescription refill data are used to compare compliance to combination items and their component medicines taken concomitantly.

1) Studies are prone to selection bias and confounding because known and unknown factors may influence prescribers' and consumers' use of combination products.

2) Consumers treated for diseases such as diabetes and coronary artery disease often receive multiple medicines within and across therapeutic classes. Assigning a single comparator to a combination item may be difficult because consumers may switch or add and subtract multiple medications within and across classes, often for good therapeutic reasons. This raises a key question: can participants in the respective cohorts switch to single-component medicines in the same class, and *vice versa*? Non-persistence with a specific item may not reflect non-persistence to a therapeutically appropriate regimen.

3) The potential for measurement bias arises in comparisons of the numbers of prescriptions between cohorts of consumers taking combination items and those taking single-component medicines. The way in which multiple prescriptions are counted and defined as co-administration can bias measures of medication possession relative to counts of single prescriptions for combination items.

4) Unintended outcomes may occur with combination items. These include "hyper compliance" (for example, where consumers continue to take the component medicines as well as the combination product); and increased wastage if non-adherence increases because of side-effects from one component of a combination item. Such unintended outcomes may misleadingly suggest improved compliance in studies based on counts of prescription refill.

In some settings, compliance may be better assessed using prospective studies or pragmatic RCTs rather than observational studies of prescription refills. The CMWG was concerned that these designs should not be discounted when considering evidence in this area. The use of alternative well designed studies that incorporate self report or clinician input may provide further critical information that is not obtainable by using prescription refill and administrative datasets. Alternatively, the use of prospective designs that incorporate some degree of randomisation of subjects may provide results that are less affected by bias, and enable studies of medicines that are not administered continuously or uniformly to be undertaken.

Interpretation and Extrapolation of Compliance Differences

Using current research methods and available datasets, it is particularly challenging to establish whether an improvement in compliance is attributable to a combination item. In addition, any short-term effect (e.g. 12 months) may not be relevant to the duration of treatment of a chronic disease. For these reasons, increases in compliance achieved by combination items (as part of a treatment plan including multiple medicines and other treatments) are difficult to translate into clinically meaningful health outcomes.

Ideally, evidence that combination items improve compliance and health outcomes would come from studies that are designed to measure both endpoints. In the absence of such direct evidence, modelling of a relationship between compliance and an intermediate outcome may be acceptable where there is good evidence that the intermediate outcome predicts longer-term health outcomes.

Financial impact (Funder or Government perspective)

Given that combination items will often replace widely-prescribed medicines for common conditions such as cardiovascular disease, there can be substantial financial implications from exempting combination items that improve compliance from future price reductions. For this reason decision makers may wish to compare estimates of the likely cost of exempting a combination medicine from future price reductions with the cost of continuing to use the individual component medicines (that are not exempt from mandatory price reductions). Such estimates will require projections of the growth in utilisation and costs for both regimens (combination and single component medicines) over four to five years or a similar timeframe consistent with other projections for Government budgeting purposes.

Context and Objectives of the Compliance to Medicines Working Group

Context

The Compliance to Medicines Working Group (CMWG) was established under the Drug Utilisation Sub Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC requested that the CMWG be established to gather information from experts and published literature on methods for evaluating and interpreting evidence used to support claims that combination products improve consumer compliance and health outcomes. The CMWG had 14 members, including representatives of the pharmaceutical industry, researchers, clinicians, consumers, DUSC and PBAC. Members are listed in Appendix 1.

In order to ensure the long term sustainability of the PBS, the *National Health Act* was amended in 2007, to include statutory price reductions for pharmaceutical items on the F2 formulary. The F2 formulary includes drugs subject to competition (multiple-branded medicines) and drugs that are part of a designated therapeutic group (TGP) where one or more drugs part of the TGP group, are multiple-branded items. The pricing of single-branded combination items is based on the individual components and therefore statutory price reductions will flow onto single-branded combination, unless there is a determination under Subsection 101(4AC)) and Subsection 99ACC(4) of the *Act.*

Evaluation of consumer compliance has become increasingly important to the PBAC since the inclusion of Subsection 101(4AC) in the *Act.* The amendment (Subsection 101(4AC)) requires the PBAC to advise the Minister for Health when the Committee determines that therapy involving a combination item (consisting of two or more drugs[1]) provides either (a) a significant improvement in consumer compliance, or (b) a significant improvement in efficacy or a reduction in toxicity compared to alternative therapies.

Under Subsection 99ACC(4) of the *Act*, the Minister may have regard to this PBAC advice when considering whether to reduce the existing agreed price of a single-brand combination item following on from a statutory price reduction of one or more of its component drugs (Submission Guidelines, Product type 1.2 p214). If claims of improved compliance are accepted, some single-branded combination items could be exempt from the flow on of statutory price reductions that have occurred in the individual component drugs. Claims of improved compliance do not, however, provide grounds for price increases to single brand combination items. As a result of these changes in the legislation, the PBAC is increasingly required to evaluate claims of improved compliance attributed to combination items, and to advise the Minister.

The PBAC also sought guidance from the CMWG on the factors that influence consumer compliance with medicines after listing. An understanding of the reasons why consumers may not be fully compliant with their drug regimens is important for achieving optimal clinical outcomes, reducing community burden of disease and ensuring the most cost-effective use of health resources. Thus compliance is relevant to the PBAC not only from a funding perspective, but also as part of its role in supporting the Quality Use of Medicines; PBAC gives feedback on compliance and factors affecting it to industry, health-care providers, government and consumers.

[1] Drugs concerned here are medicinal products that are assessed as independently effective compared to placebo by the TGA

Objectives
The objectives of the CMWG were to:

- Define terms relevant to the investigation of compliance to medicines.
- Identify factors that affect the measurement of compliance and the interpretation of measurement data.
- Describe relevant methods of measuring compliance.
- Explore and identify the limitations of the commonly-used study designs and analytical techniques in the assessment of compliance to medicines; in particular retrospective observational studies of prescription refills.
- Examine the implications of relying on Australian versus non-Australian sources of evidence and using existing administrative databases rather than other approaches such as prospectively collecting data.
- Specify the evidence needed to support clinically meaningful differences in compliance.
- Provide the PBAC with information and advice on assessing the quality and validity of evidence used to support claims of increased compliance with alternative forms of medicine (including combination items).
- Identify the most appropriate forms of evidence for assessing compliance.

The CMWG, at its initial meeting decided that the report should be broadened to include information relevant to measuring and assessing compliance to medicines and the effect on health outcomes. I.e. the aims of the CMWG are broader than the initial terms of reference (see Appendix 1) that were developed specifically to address only the issues arising from the addition of Subsection 101(4AC) to the *Act*. The Group was concerned that any assessment of compliance to medicines be undertaken in context, and that complexity of this context needed to be explored within the report. It was also considered important to assist PBAC by providing information on the broader issues of measuring and assessing the impact of compliance on health outcomes.

It is beyond the scope of this report to provide guidance on the preparation or evaluation of a submission to the PBAC claiming a compliance advantage. Rather, the report provides information to assist with the interpretation and evaluation of evidence to support claims of compliance, particularly from comparative studies of compliance to different medicines or formulations.

This report is largely technical. It addresses the specific issues of research design and data analysis that will assist in the evaluation of research on compliance. The CMWG considered that a separate, less technical paper might be useful for a broader readership, including consumers.

Methods used to prepare this report

A narrative literature review was undertaken, drawing on key authors and publications identified by expert members of the CMWG and on literature reviews of adherence or compliance done by the UK National Institute of Clinical Studies (NICE), International Society for Pharmacoeconomic and Outcomes Research (ISPOR) and the World Health Organization (WHO). Given the existence of these reviews and resource constraints for the preparation of this report, the CMWG did not attempt to undertake a current systematic literature search.

Three face-to-face meetings of the CMWG were held over a 12-month period. The initial meeting identified the scope and developed a draft framework for the report. Numerous teleconferences and discussions with individual CMWG members contributed to the preparation of the report and the key information that should be conveyed to the PBAC and other users of this report.

Introduction

The PBS provides subsidises medicines that are cost effective and improve health outcomes for Australians. Compliance with medication regimens is one factor that can influence the achievement of health outcomes and affect the cost-effectiveness of a medicine. Understanding the reasons why consumers may not comply optimally with their medication regimens and what interventions improve compliance is important in ensuring that the health outcomes demonstrated in clinical trials are realised by consumers in all settings. Evidence on the extent of non-compliance and its effect on clinical outcomes is of concern to all those who are involved in the provision of health care. Importantly the PBAC and the Australian Government need this evidence to make recommendations and decisions around funding and negotiating prices for medicines that are to be listed on the PBS.

The term 'compliance' and its relationship to other terms describing individuals' use of medicines (such as 'adherence', 'persistence' and 'concordance') is ambiguous. Part A1 presents a definition of 'compliance' that was endorsed by the CMWG and is used throughout this report.

Identifying reasons why individuals or a specific population do not, or cannot, comply optimally with a medication regimen is central to assessing the potential benefits of interventions to improve compliance. Factors that influence compliance are discussed in Part A3. Many interventions, ranging from better consumer education and support to modification of the medicine or medication regimen, may improve compliance. With regard to the latter, a wide range of strategies are employed. These include reducing the frequency of administration (e.g. extended- release formulations, or selection of agents with a long half-life), reducing pill burden and/or cost (e.g. fixed-dose combination products) and modifying packaging or presentation (e.g. dose administration aids, pre-filled syringes). Assessment of fixed combination products to improve compliance is a particular focus of this report.

The field of research on compliance with medicines is rapidly evolving; with many new methods being developed to assess compliance. Part B of this report reviews methods to measure and assess compliance and provides information on the strengths and limitations of these methods. An emerging area of research has been the analysis of data on prescription refills from pharmaceutical and administrative health databases to assess consumer compliance. Quantification of prescription refills has become a common surrogate measure for medication compliance. However much of this research is from the USA and other countries where systems for funding pharmaceuticals and health care differ from the subsidised system in Australia.

The medicines compliance literature has not yet extensively compared rates of compliance between consumers prescribed combination items and those prescribed their component medicines concomitantly. As yet, no consensus exists among pharmaco-epidemiologists on how to conceptualise and measure the effects on compliance of two or more component drugs when taken concomitantly versus a combination product. In order to inform the PBAC the CMWG has developed a framework for assessing evidence to support claims of improved compliance to combination products relevant to *Subsection 101(4AC)* of the *Act* in Part C of the report. Part C also explores the complexities of defining comparator therapies and the methods to measure compliance specific to combination items.

The report concentrates on assessing compliance to medicines as prescribed. It does not assess concordance of prescribing with best practice or clinical guidelines or provide guidelines for practice.

Part A Definitions, Perspectives and Factors Influencing Compliance to Medicines

Part A reviews terminology and definitions relating to compliance and its synonyms and presents the definitions agreed by the CMWG. To assist PBAC in interpreting studies of changes in compliance the report provides context for consideration of compliance from the perspectives of the consumer, the prescriber and the funder (i.e. the Australian Government). The report also provides information on many of the factors identified in the published literature that potentially influence compliance.

A.1 Defining Compliance to Medicines

Key points

- *Compliance is a composite of acceptance, adherence and persistence*
- *Consumers are central to all aspects of compliance to medicines*

Defining compliance is difficult, confusing and contentious. The term *compliance* is used in many different situations and many related terms exist which are viewed interchangeably at times (Cramer, 2007; Bissonnette, 2008). No single definition of compliance encompasses all aspects of consumer behaviour related to medicine taking. A range of terms that include compliance, adherence, persistence, concordance and acceptance (Heath, 2003; Segal, 2007) are regularly used in the literature. These terms refer to the shared decision between a prescriber and consumer, and for the consumer to undertake an agreed action such as taking a medicine or adhering to a dietary or exercise regimen. Such an agreement includes consideration of consumer values and the risks and benefits of the various treatment options. (NPS, 2007; Wahl, 2005; WHO, 2003; Urquhart, 2001).

Australia's National Medicines Policy identifies consumers as key partners in achieving health outcomes. It states that:

> "each partner accepts that all must be engaged in a cooperative endeavour to bring about better health outcomes for all Australians, focusing especially on people's access to, and wise use of medicines."

The National Strategy for Quality Use of Medicines goes on to identify "the primacy of consumers" as a principle that underpins the quality use of medicines. It states:

> "the Strategy recognises the central role of consumers in attaining quality use of medicines and the wisdom of consumers' experience. Consumer involvement in all aspects of the Strategy is critical"(Commonwealth Department of Health and Ageing, 2002 p7).

Agreement of all parties appears to be a critical element in compliance. The published literature provides some basis for the assumption that, where the agreement cannot be maintained, the desired health benefit is unlikely to be achieved (Cramer, 1995, 2007a).

To measure the extent to which compliance is attained in practice, it is necessary to invoke three concepts: acceptance, adherence and persistence (WHO, 2003; Caetano, 2006; Kothawalla, 2007).

The following definitions were accepted by the CMWG for the purpose of this report, in which the agreed regiment refers to taking medicine:

Acceptance: The consumer's informed decision to undertake behaviours that are expected to lead to improved health outcomes. In this report medicine taking is assumed to be part of the agreed regimen. (WHO, 2003)

Adherence: The extent to which the consumer conforms to the agreed behaviours, with respect to timing, dosage and frequency of medication taking. (Cramer, 2007a)

Persistence: The duration of time from initiation to discontinuation of therapy. (Cramer, 2007a)

In this report, the term '*compliance*' has been used in the broadest sense to encompass all aspects of consumers' acceptance, adherence and persistence with a prescribed medicine regimen.

A.2 Perspectives on the Importance of Compliance

A.2.1 Overview

It is important to consider the perspective from which compliance is considered: that of the consumer, the health professional; or the payer (funder). In many situations the priorities of the consumer and prescriber may be different in relation to taking medicines (Britten, 2003). The appropriate level of compliance for an individual can be highly variable and may not be the same as the 'optimum level' of compliance at a population level that is assumed or considered appropriate by a prescriber or funder. Therefore consumers, health professionals and funders will often have different views on the desired level of compliance and extent to which actual compliance should match optimal compliance in order to achieve intended health outcomes.

In addition the relationship between compliance and health outcomes is not uniform across individuals and different medicines. The relationship between varying degrees of compliance and the incremental effect on health outcomes is complex and effected by many factors such as individual response, pharmacokinetics, underlying disease severity and other lifestyle factors.

A2.2 The Consumer Perspective

Key points

- *The relationship between health professional and consumer influences compliance.*
- *The applicability of the medicine regimen to individual consumers' circumstances may change over time due to variability in responsiveness, adverse effects, drug toxicity or the availability of alternative or superior treatments.*
- *Consumers can organise their medicine taking around their own priorities without reference to health professionals, and this does not necessarily lead to poor health outcomes.*

- *Availability of clinically appropriate and safe combination medicines addresses one of many factors associated with the consumer's choice of whether to adhere to or persist with medicines.*
- *Consumers value advice from variety of health professionals about their medicines.*

The consumer perspective refers to the relationship between the individual, the health professional and the tailoring of treatment to the individual's specific medical condition and personal circumstances.

Pound et al (2005) conducted an extensive literature search over 10 years identifying qualitative studies on consumer (lay) experiences of medicine taking. Findings of this review were synthesised into three parts as follows:

I. The ways in which consumers evaluated their medicines. Consumers considered benefits and costs, adverse events and how well the regimen fitted with their daily routines. Several studies reported instances in which people ceased taking their medicines in order to evaluate their effects.

II. Medicines and identity. Many studies found that people equated taking medicine with being ill. People who do not accept the severity of their illness may not accept the need to take their prescribed medicines. Many medications carry perceptions of stigma, particularly those used to treat conditions that people are not comfortable disclosing publicly such as mental illness, HIV and certain other infections.

III. The ways in which consumers take their medicines. Most people disliked taking their medicines and tried to minimise their intake. Many people also adjusted their regimens to reduce adverse effects or avoid addiction while still realising some therapeutic gains. This may have involve reducing doses, omitting doses or taking 'drug holidays' to reduce the 'build-up of toxicity' or to 'cleanse' their bodies. Some also reported reducing doses because they could not afford the prescribed amounts.

This study concluded that a major reason why consumers do not take a medicine was concern about the medicine itself and its side effects. They noted:

> "On the whole the findings suggest that there is considerable reluctance to take medicine and a preference to minimise medicine intake." (Pound et al, 2005, p151)

The variety of strategies adopted by consumers to manage or modify their medicine intake illustrates consumers' varying degrees of resistance to taking medicines. The varying degrees of resistance also reflect the differing perceptions between prescribers and consumers of medicine-related risks and benefits (Jones, 2003).

In Australia, an individual consumer may have multiple prescribers and other health-care professionals who may interact in various ways with the consumer that influence compliance. (Jones, 2003). Consumers value health professionals who spend time discussing their medications with them. Because of time constraints, consumers may feel that health professionals do not convey enough information about their medications. Consumers also appreciate open communication between various health discipline groups (for example, between general practitioners and pharmacists) as a means to pre-empt any potential problems that may arise (Manias et al, 2007).

Compliance to medicine regimes may vary with the type of disease and the extent to which a consumer understands the properties of a medicine. Prescribers and consumers tend to have more concern about non-adherence for certain types of medicines. These include medicines with narrow therapeutic windows (e.g. warfarin) or where the adverse consequences of non-compliance are well recognised and have a relatively rapid onset e.g. antiretrovirals, anti-tuberculosis therapy. Conversely, compliance with some medicine regimens is perceived or recognised as less critical e.g. occasional lapses in compliance with long-term management of hypertension or hyperlipidaemia to prevent cardiovascular disease.

For individual consumers, it may be appropriate to vary their compliance in response to certain circumstances. These include the occurrence of side effects or adverse events; the need to take a course of another medicine which has undesirable interactions; and the need to undergo another form of treatment (such as surgery) in which the medicine is contra-indicated. Titration of some medicines is also required in treatment of many diseases. Individual variations occur between consumers in response to most medicines, arising from pharmacodynamic and pharmacokinetic factors which may result in variations from the doses recommended in therapeutic guidelines or product information. In particular, where a medicine is titrated to a specific response or biochemical measure, the quantities required and frequency of dosing can vary considerably between consumers. Consequently, studies of compliance in these situations depend on accurate records of doses taken and relevant biochemical data.

A2.3 The prescriber or health professional perspective

Key points

- *When prescribing a medicine, prescribers consider a wide range of factors, such as the complexity of the regimen, their assessment of the consumer's level of understanding, and the cost.*
- *The involvement and level of understanding of other health professionals can influence the consumer's agreement to take, and level of compliance to, prescribed medicines.*
- *The availability of combination products adds choice and reduces pill burden but is potentially associated with confusion for health professionals and consumers.*

The health professional perspective includes (but is not confined to) the prescriber perspective. The prescriber perspective is expressed through the prescriber's therapeutic decision-making process which is expected to take account of the consumer's needs and preferences, best-practice recommendations, the approved indications for a medicine, benefits and side-effects. The prescriber is also influenced by prior experience in using a medicine, the cost to the consumer and the use of public resources.

The principles that underpin the perspectives of other health professionals are likely to be similar to those of the prescriber. However, other health professionals may interpret these principles differently, or base their perspectives on different observations and experience. For example, if a health professional other than the prescriber is more actively involved in administering the medicine and/or caring for the consumer on a particular medication regimen, he or she may have a different appreciation of the benefits and adverse effects and subsequently offer conflicting advice.

The relationship between the prescriber and consumer is a significant factor in promoting compliance with medicines (Heath, 2003). Compliance has been found to improve if: the relationship is based on trust; time is spent discussing the benefits of compliance; information is given to consumers; and co-ordination of care is ensured (Manias, 2007 and Jones, 2003).

Co-ordination is particularly important if a consumer sees a large number of prescribers, including specialists and other health professionals. Such situations may lead to confusion, multiple prescriptions and greater risk of adverse events.. In secondary analyses of a cohort study, Green et al (2007) sought to determine whether the number of physicians prescribing medicines to elderly consumers was associated with consumers' likelihood of reporting an adverse drug event. They found that each additional provider prescribing medicines increased the odds of a reported adverse event by 29% (odds ratio 1.3; 95% CI, 1.0–1.6). They suggested that this could be due to poor communication among the multiple prescribers and recommended that physicians should ensure more effective coordination of care, including communication about all medicines prescribed.

Prescribers consider many factors when selecting the best available medicine for a consumer (Betancourt et al, 1999). These factors include: the prescriber's understanding of consumer's concept of their illness; the prescriber's assessment of the consumer's ability to afford the medicine or physically obtain a prescribed medication; the prescriber's understanding of the consumer's fears, beliefs and concerns about taking medications; and the prescriber's attempt to communicate in different ways to overcome barriers. Examples of such barriers include consumers with culturally and linguistically diverse backgrounds and those with lack of social supports. The prescriber's view of a consumer's understanding about the importance of compliance affects the choice of medicine; for example a prescriber may avoid high-risk (associated with non-compliance) therapies for some consumers (NICE, 2009).

The availability of combination medicines provides additional options for prescribers. To date little research has been published to help prescribers in assessing the risks and benefits of improving compliance through the use of combination medicines to simplify the drug regimen compared to the individual components or other drugs in the same therapeutic class (Moulds, 2001). For example, combination medicines may not be therapeutically ideal replacements for some consumers while promoting better management in others. Thus a prescriber may need to choose between convenience and the optimum regimen (Phillips et al, 2001). As more and more combination items are available, prescribers' awareness of the large range of alternatives will be challenged.

A2.4 The funder or Government perspective

Key Points

- *In subsidising medicines, the Government considers the consequences of a change in the availability of a medicine or formulation in return for improved compliance, costs and health outcomes.*
- *The determination of what is an 'appropriate' or 'optimal' level of compliance may differ between the societal perspective (represented by the funder) and the individual's perspective.*
- *While findings from health technology assessments are increasingly considered in funding decisions, health benefits resulting from improved compliance are often assumed in health technology assessments rather than demonstrated.*

- *The data sources and methods for considering compliance within health technology assessments are limited.*

In Australia, the funder perspective is principally that of the Australian Government. Since 1999, the Government has endorsed a National Medicines Policy to meet medication and related service needs in such a way that optimum health outcomes and economic objectives are achieved. The listing of medicines on the PBS provides for the provision of, and timely access to, medicines required by Australians at a cost that individuals and the community can afford.

In many developed countries, including Australia, the role of health technology assessment in funding decisions is increasing (Stolk et al, 2009). Health technology assessments do not routinely consider compliance. However, as the role of consumers in these processes develops, the assessments of medicines may be expected to provide more or better evidence on compliance and any associated health benefit.

When a medicine is PBS funded, the extent to which subsequent compliance differs from that in the trials (on which evidence for listing was based) may be a factor in altering the health benefit gained. If compliance with a medicine is sufficiently low that the expected health benefit is reduced, PBS listing of the medicine will not yield the outcome for the Australian community that was expected on the basis of the evidence presented to PBAC at the time of recommendation. Conversely, if the current level of compliance at a population level for a medicine is reasonably high, there may be little scope to further improve health outcomes by increasing compliance.

In Australia, the PBAC is expected to advise the Minister when it determines that therapy involving a combination item provides either a significant improvement in consumer compliance or a significant improvement in efficacy or a reduction in toxicity compared to existing therapies (*National Health Act* Sub-section 101(4AC)). In addition, when the PBAC is considering applications to list medicines, the health technology assessments provided may include a 'value' associated with a compliance advantage. Determination of the 'value' requires evidence that the improvement in health outcome is likely to be attributable to the improvement in compliance resulting from the use of a particular form of medicine.

A2.5 Relationship between compliance and health outcomes

Key Points

- *The relationship between compliance and health outcomes is complex and multi-factorial.*
- *People who are compliant with medicines are more likely to show improved treatment and health outcomes.*
- *To date, methodological difficulties have impeded the study of relationships between compliance and health outcomes. For example, it has not been possible using observational data to establish a causal relationship between a particular form of medicine, its effect on compliance, and its ultimate effect on health outcomes.*
- *It is difficult to establish the magnitude of the effect of compliance (measured in a defined timeframe such as 12 months) on longer- term health outcomes.*

- *Statistically significant differences in measured levels of compliance do not necessarily translate into clinically meaningful differences in treatment or health outcomes.*

It is clearly important for people to take medicines in order for the medicines to work (Koop in Bonaccorso, 2003). However the relationship between varying degrees of compliance and the incremental effect on health outcomes is complex.

Published literature shows that understanding of the relationship between varying degrees of compliance and treatment or health outcomes is limited; due in part to different ways of measuring health outcomes. For example, some health outcomes such as pain and anxiety are subjectively assessed through consumer self reports, while others are assessed with one or more objective measurement scales (DiMatteo, 2002).

On balance compliance with therapy has been shown to have a positive effect on intermediate treatment outcomes, which are surrogates for longer-term health benefits (Simpson, 2006; McDermott, 1997; Shepherd, 1995; DiMatteo, 2002). A meta-analysis of 63 studies that examine the effect of improved adherence to therapy on treatment outcomes showed that adherence (compared with non-adherence) reduced the risk of a null or poor treatment outcome by 26% (standardised risk difference). The odds of achieving the study outcome if the consumer was adherent were almost three times higher than the odds of achieving the study outcome if the consumer was non-adherent (DiMatteo, 2002).

Despite the overall consensus in the literature that higher levels of compliance usually predict improved consumer outcomes, this effect has only been reported for widely different levels of compliance. There is currently little evidence that smaller compliance increments also affect health outcomes and, if so by how much. A long term cohort study of persistence with statins reported that consumers whose records indicated the proportion of days covered (PDC) to be greater than 90% had a 45% reduction in risk of death compared to consumers whose records indicated the PDC was less than 10% (Shalev, 2009). Another study (Dragomir, 2009) reported that a consumer group with low adherence (measured as mean medication possession ratio [MPR] of 42%) had more severe cardiovascular disease and hospitalisations than those with high adherence (mean MPR of 96%).

Protease inhibitors used for the treatment of HIV is one of a few classes' of medicines for which the level of adherence needed to produce an adequate therapeutic effect has been demonstrated. Paterson et al (2000) conducted a prospective observational study designed to assess the effects of different levels of adherence to therapy on virologic, immunologic, and clinical outcome. Virologic failure was documented in 22% of patients with adherence of 95% or greater, 61% of those with 80% to 94.9% adherence, and 80% of those with less than 80% adherence. Patients with adherence of 95% or greater had fewer days in the hospital (2.6 days per 1000 days of follow-up) than those with less than 95% adherence (12.9 days per 1000 days of follow-up; P = 0.001). No opportunistic infections or deaths occurred in patients with 95% or greater adherence.

The relationship between compliance and health outcomes is affected by the pharmacodynamic properties of individual medicines. For medicines with long half lives (e.g. angiotensin converting enzyme (ACE) inhibitors, depot extended-release formulations such as risperidone injection and transdermal formulations such as fentanyl patches) and those medicines not dependent on critical plasma concentrations for maximum effectiveness

(e.g. thiazide diuretics) the relationship between adherence and health outcomes may be more variable. For such medicines a clinically important effect may be demonstrable only with a larger difference in measured compliance.

While randomised control trials (RCTs) provide information on efficacy, the measurement of effectiveness in routine practice is more difficult. Most RCTs do not consider compliance as a factor within the trial design and are not specifically designed to evaluate the effect of compliance on outcomes. Indeed consumer selection criteria in RCTs can bias results towards better compliance. As RCTs are not generally designed to assess compliance observational studies are often used for this purpose. However, if observational studies of compliance do not include measurement of health outcomes, it is difficult to attribute any change in health outcomes to compliance alone.

A3 Factors that Influence Compliance

Key Points

- *A large number of factors may influence compliance to medicines.*
- *Not all of the factors that influence compliance are quantifiable (e.g. some specific consumer characteristics and beliefs): it may therefore be difficult to control for them in observational research.*
- *The effect of any one factor on compliance cannot always be predicted, and should be assessed in the context of the specific population using the medicine.*
- *The presence of non-compliance in a population is likely to be affected by a combination of factors; the putative causal factors may account for only a small proportion of the variability in compliance.*
- *The use of once-daily formulations and combination products do not by themselves ensure improved compliance.*
- *The health care setting or environment where medicines are taken can significantly effect compliance.*

The CMWG identified several published reviews of factors that influence consumer compliance to medicines: Pound et al, 2005; Krueger et al, 2005; Jackson et al, 2006; DiMatteo, 2004, and NICE, 2009. The following is based on these major reviews.

Evidence on the effects of various factors on compliance is often conflicting. This may be due to the plethora of study designs used (covering the spectrum from qualitative studies to RCTs), differences among the populations studied and the use of different methods to measure compliance. Such variations limit the conclusions that can be drawn about the direction of the effect on consumer compliance, particularly at a population level.

Table 1 below is an adaptation of two reviews that examined a large number of studies of factors (variables) affecting compliance, (Jackson, 2006, Krueger, 2005). The table gives the number of studies that found an overall affect on compliance for each variable.

Table 1: Studies reporting effects of selected consumer and regimen variables on compliance.

Variable	Number of studies reporting an overall effect on compliance – Number and the direction of the effect		
	Increase	Decrease	No effect
Consumer variables			
Increasing Age	13	5	35
Female Gender	5	3	31
Living Alone	3	2	13
Married	2		8
Family/ social support	5		1
Higher Education	4	1	8
Knowledge of disease/treatment	4		7
Prescribed by specialist	2		
Number of recent medical visits	4		
Positive consumer-provider relationship	14		3
Cognitive impairment	1	9	3
Poor perceived health status	1	3	5
Unhealthy behaviours or substance abuse		4	3
Depression/anxiety/ stress	3	14	
Regimen variables			
No of drugs >3	1	20	13
Regimen complexity		9	6
Difficult container		3	1
Side Effects or fear of		9	1
High cost of drugs		4	

Source: Adapted from Jackson, 2006, p12 and Krueger et al (2005)

Evidence of the effect of age on compliance is conflicting. This may reflect different populations of consumers with different conditions within the older age groups. Those who are well supported in the community with carers and family, reside in residential care facilities, or have access to subsidised medicines and dosing aids, may be more compliant with their medicines than older people who are isolated, forgetful, poorly supported and lacking access to affordable medicines. In a large meta-analysis (DiMatteo, 2004) reporting correlations between adherence and consumer demographic variables, the relationship between adult age and compliance was not significant. However compliance had a negative association with age in the paediatric studies, adolescents being less compliant than younger children. Similarly there was no significant relationship between gender and compliance in adults but girls were more likely to be compliant than boys in paediatric populations. The relationship between level of education and compliance was found to be positive and stronger in the treatment of chronic illness than acute illness. Income and socioeconomic status were also positively associated with compliance, with income having a stronger effect than socioeconomic status.

The United Kingdom (UK) National Institute of Clinical Excellence (NICE) Adherence to Medicines Guideline Development Group (GDG) specifically reviewed published evidence on interventions that increase adherence or compliance. Although regimen complexity is thought to be associated with poor compliance, the quality of the available evidence to show that reducing regimen complexity improves compliance is poor (NICE, 2009). Combinations of two or more drugs are also assumed to improve compliance through convenience and reduction in costs for consumers, but again only limited evidence is available to support this. Interestingly some studies involving consumers with hypertension (Osterberg, 2005) and Type 2 diabetes (van Bruggen, 2009) have found that minimising the frequency of doses has a greater effect on compliance than minimising the total number of medicines taken concomitantly. The NICE GDG recommendation is:

> "that changes to dosing regime need to be tailored to the needs of the individual patients. The GDG considered that evidence does not support that developing once-daily formulations and combined pills necessarily improve adherence." (NICE, 2009, p210)

Not surprisingly, the emphasis of research on the relationship between the costs of medicines and compliance varies among different countries. Cost has been shown to be a significant factor in developing countries and in the USA. In contrast, in the UK and Australia, most prescribed medicines are subsidised by governments and relatively few studies have been undertaken. Some evidence exists to show that cost may be a concern for some consumers in Australia: a rise in consumer contributions (co-payments) was observed to have been followed by a significant reduction in the use of common medicines (Hynd, 2006). Cost concerns may also raise doubts among consumers about the value of a prescription (NICE, 2009).

Most of the variables discussed above are quantifiable and easily extracted from health or administrative datasets that include consumer demographic characteristics and treatment regimens. This makes it possible to measure the effects of these factors at a population level. However, these variables do not explain individual consumer's reasons for non-adherence.

As noted in Part A2.3, the individual's unique beliefs and behaviours relating to the taking of medicines also affect compliance in ways that are not easily measured. A review of qualitative research in this area concluded that consumers on the whole are reluctant to take medicines for extended periods and that they often seek to minimise their medicine intake (Pound, 2005). Consumers' perceptions of the benefits and side effects of a particular medicine, and the way in which the use of a medicine fits with their lifestyle, all influence compliance.

Individual consumer's self esteem and self image have also been shown to influence their acceptance of treatment and readiness to follow medical advice. Consumers with low self esteem may equate taking medicine with physical or psychological weakness. Under these circumstances, the consumer may 'use' non-compliance as a 'test' to determine whether the illness is still present or as a means for enhancing control (Morris, 1993).

The views of consumer can be reflected in prior behaviour with respect to compliance with medicine. Cramer (1995) found that an individual's past compliance behaviour is a strong predictor of future behaviour with respect to medicine taking.

As stated in A2.3, the relationship between the prescriber and consumer is a particularly important factor in promoting compliance with medication. Ideally prescribers' communications with consumers should facilitate the development of positive therapeutic alliances in order to promote medication compliance. Taking the time to explain reasons for taking medications and their potential side effects can assist in improving medication compliance (Marder et al, 1983).

The CMWG identified two additional factors that significantly affect compliance to medicines and that should be considered when interpreting studies assessing interventions to increase compliance:

- The environment or setting in which the medicine is used, e.g. the proportion of consumers in aged-care facilities where medicines are administered by staff *versus* self administration in the community.
- Current media publicity, promotional marketing, and consumer support programs provided by the pharmaceutical industry and other organisations such as the National Prescribing Service, Governments, pharmacies and disease advocacy groups.

Government and population-level initiatives can significantly influence compliance. The Government can use various approaches, such as consumer education interventions, to promote understanding of the benefits of medicines, or even provide direct financial incentives. For instance, as part of the Medicare Benefits Scheme, practice nurses and allied health professionals are able to provide up to five consumer education sessions for complex chronic disease management. In these sessions, they can conduct ongoing monitoring of current treatments including medicines and consumer education. Accredited pharmacists can also play an important role in promoting quality use of medicines by undertaking home medicines reviews (Medicare Australia, 2009). Such incentives are used to support the development of care plans and other initiatives which could lead to improvements in compliance.

In summary, many diverse factors may affect a consumer's decision to take a medicine, however only some of these factors are related to the medicine itself and different types of formulations. These factors affect different consumers to differing degrees within and between populations. Understanding the effects of such modifying factors on compliance for the population concerned is critical to the correct interpretation of the research.

Part B: Measuring and Assessing Compliance

Part B examines the question of how to measure compliance and differences in compliance that could be attributable to differences among pharmaceutical products. It also examines ways of valuing, in economic terms, the effects of different levels of compliance on health outcomes.

Key points

- *Compliance to medicines is difficult to measure, particularly when assessing compliance with long-term, self-administered therapies.*
- *The hierarchy of evidence often applied to studies of medicine efficacy and safety does not necessarily apply to studies of compliance.*
- *A priori registration and or publication of study protocols should be encouraged to improve the quality of evidence from studies of compliance.*
- *Variations in the methods used to measure compliance limit comparison and interpretation of the results.*
- *Different approaches to measuring compliance often produce results that correlate with one another, but they rarely produce the same estimate of overall compliance.*
- *The advantages and disadvantages of the design and methods used in any study of compliance need to be considered when interpreting the results from such research, as must the context in which these results are derived.*
- *Studies estimating compliance should use continuous rather than ranked or dichotomous variables. They should present more than one measure of compliance and, where possible, include measures of self-reported compliance.*
- *Research linking health outcomes with compliance is likely to be informative to the clinical interpretation of changes in compliance.*

B1 Overview

Consumers are often considered to be either compliant or not compliant to medication regimens. However, the reality is much more complex. For example, consumers may persist with a regimen for a short period of time, or may partially adhere to a regimen, or may persist but only partially adhere. This makes the measurement of compliance and the interpretation of data on compliance difficult, particularly when assessing long-term self-administered therapies. Although compliance is often reported as a dichotomous variable (compliant versus non-compliant), the extent of compliance is in practice a continuum from zero compliance to more than complete or full compliance (i.e. taking more than the prescribed amount of medication).

Several methods are available for measuring acceptance, compliance, adherence and persistence. These methods can be broadly classified as direct or indirect. Direct methods involve observing consumers taking medicines or measuring the amount of a medicine or its metabolite in body fluids or tissue. Such methods are expensive and invasive, and they mostly reflect recent compliance only. Indirect methods include consumer questionnaires (self-report or investigator- or clinician-administered), pill counts, medical record or chart reviews and electronic medication monitors. Such methods tend to overestimate compliance because the amount of drug taken is not known (e.g. pill ‘dumping’ or wastage cannot be quantified). Consumer reports or diaries are subject to bias in the recording of the amount

and timing of medication (e.g. if they are filled out retrospectively before an appointment, rather than – as requested – when medicines are taken). Data collection from self report is usually conducted over short time periods (days or weeks) and enrolment in a study may influence adherence behaviour.

With the widespread adoption of electronic prescribing and electronic recording of prescriptions by pharmacies and funding agencies, prescription refill has become a popular surrogate measure of consumer adherence and persistence. The main benefits of using prescription refill datasets are that adherence and persistence can be estimated for large numbers of consumers over long periods of time relatively cheaply. The main disadvantage is that refill data do not show whether or not consumers take medicines in accordance with the prescribed regimens. An important advantage is that, where prescription refill datasets can be linked to or include health outcomes, such as mortality, the potential exists to assess the relationship between compliance and health outcomes.

The traditional hierarchy of evidence for the efficacy and safety of medicines may not apply to studies of compliance. While the RCT is usually the best design for assessing efficacy, RCTs offer internal validity at the expense of external validity. As research on compliance specifically seeks information on how medicines are taken by the consumer in practice, observational studies or specially-designed prospective or pragmatic trials that combine the advantages of randomisation and follow-up in everyday (rather than formal RCT) settings may offer stronger evidence in relation to consumer compliance. Moreover, blinded RCTs of compliance are difficult to design because blinding of subjects to physically different formulations or different regimens is difficult.

The choice of study design must be appropriate to answer the specific research question on compliance. Different designs may offer different advantages for different questions on different medicines in different settings. In recognition of this, the CMWG tabulated the various study designs that have been employed and their strengths and weaknesses, to measure a variety of aspects of consumer compliance (Table 2).

Table 2: Study designs for measuring compliance to medicines

Study design/type	Method of assessment	Strengths	Limitations	End points /outcome measures
Randomised Control (or Explanatory) Trials (RCT)	All randomised studies.	**1.** Randomisation reduces bias and yields the strongest and most direct evidence of the effect of the intervention in the trial population.	**1.** Trial participants may behave differently when they know they are under observation. **2.** Recruitment bias. **3.** Possibility of large loss to follow-up and small number of participants. **4.** Limited transferability to other populations, for example those with multiple chronic conditions or at either end of the lifespan.	
	Direct measures: Directly observed.	**1.** Potential observation or reporting bias.	**1.** Intrusive.	**1.** Amount of Medicine taken.
	Measurement of medicine/biomarkers in body fluids.	**1.** Accurate and objective.	**1.** Expensive, invasive and short term. **2.** Only provides an assessment of recent compliance.	**1.** Biochemical measurement or level.

Table 2: Study designs for measuring compliance to medicines (Cont)

Study design/type	Method of assessment	Strengths	Limitations	End points /outcome measures
Randomised Control (or Explanatory) Trials (RCT)	**Indirect measures:** Self report, Questionnaire for caregiver.	**1.** Potential for information on all aspects of compliance (acceptance, adherence and persistence). **2.** Relatively accurate if valid and reliable measures used.	**1.** Subject to reporting bias. 2. Factors other than medication adherence can influence consumer response. **3.** Positive response bias possible which decreases sensitivity of self report.	**1.** Amount of Medicine taken Or doses missed.
	Pill counts.	**1.** Inexpensive and relatively quick to complete. **2.** Can give information on adherence and persistence.	**1.** Potential for pill 'dumping'. **2.** Possession may not reflect intake. **3**. Reliance placed on participants informing researchers of the dates when containers were opened and commenced. This information may not be accurate.	**1.** Amount of Medicine taken Or doses missed.
	Electronic medication monitors.	**1.** Can overcome potential problem of 'pill dumping'. **2.** Can be connected to computer software to obtain graphical representations of administration trends.	**1.** Expensive, especially if several medications need to be monitored, and require consumer co-operation.	**1.** Medication taken and timing/pattern of doses.
	Measurement of clinical response /treatment outcomes.	**1.** Must incorporate both compliance measures and clinical outcome measures.	**1.** Clinical response may be due to other factors than compliance to medicine (e.g. pharmacogenetic profile, placebo response). **2.** Outcomes should not be used as proxies for adherence.	**1.** Changes in treatment response e.g. B/P.

Table 2: Study designs for measuring compliance to medicines (Cont)

Study design/type	Method of assessment	Strengths	Limitations	End points /outcome measures
Pragmatic randomised trials	Prescription refill administrative data Prescriber data May include clinical and consumer related data from surveys.	**1.** Reflect the heterogeneity of consumers in clinical practice. **2.** Exclusion criteria are kept to a minimum – co-morbid medical conditions are a common feature. **3.** Randomisation minimises the effects of bias due to confounding.	**1.** Potentially longer follow-up or clinically relevant follow-up for assessing persistence to shorter term therapies. **2.** It may be difficult to obtain blinding of the intervention. **3.** May be difficult to obtain ethics approval.	**1.** MPR PDC **2.** Time without medication **3.** Coverage gap analysis **4.** Persistence curves **5.** Mean days to refill.
Observational cohort studies	All observational studies.	**1.** Timely and less expensive Provides for "real world" experience with the medicine.	**1.** Subject to selection bias and unknown confounders. **2.** Limited by capture and quality of the dataset.	
	Chart review.	**1.** Provides information on dosing.	**1.** Specific to time under supervision/care Quality of information depends on accuracy of documentation	**1.** Doses missed.
	Prescription refill In health administrative databases.	**1.** Objective, easy to obtain data and analyse. **2.** Large populations can be studied. **3.** Allows for longitudinal trends to be evaluated. **4.** Potential to link to other health datasets.	**1.** Possession may not equal intake. **2.** In the case of pharmacy records, consumers must source medication from same pharmacy (group/system e.g. PBS). **3.** Dose regimen is usually assumed. **4.** May not include dosing/timing or clinical data – limited use in measuring adherence. **5.** Only apply to a medicine post registration that has been on the market for a clinically meaningful period of time. **6.** Errors or inaccuracy in data.	**1.** PDC days of coverage. **2.** MPR number of scripts refilled. **3.** Time without medication or gaps in medicine possession. **4.** Mean days to refill. **5.** Persistence using sequential prescription refills, survival curves (Kaplan-Meier) or anniversary models.

Table 2: Study designs for measuring compliance to medicines (Cont)

Study design/type	Method of assessment	Strengths	Limitations	End points /outcome measures
Nested Case Control	Within administrative datasets or Pharmacy refill data.	**1.** Potential to provide additional clinical information and reasons for non-compliance. **2.** Potential to measure adherence in selected cases.	**1.** More time consuming and expensive as must be designed prospectively.	**1.** Any of the above endpoints used in observational or RCTs.
Descriptive or Qualitative Studies	Interviews with consumers or Health professional Focus groups.	**1.** Give insight to facilitators and barriers to compliance and persistence. **2.** Information can be used to assist in the development of interventions aimed at improving compliance. **3.** Information can be used in development of validated tools to assess adherence and persistence.	**1.** Interviews and focus groups do not provide details on level of adherence or persistence present. **2.** Time consuming process if seeking to obtain views from different individuals and perspectives.	**1.** Consumer or health professional perspectives and experiences. **2.** Applicability /transferability associated with individuals in a similar context.

B2 Randomised Studies of Compliance

Key Points

- *Randomised trials can play a role in measuring the impact of interventions to improve compliance.*
- *Many existing RCT designs have limitations when measuring levels of compliance and the effect on health outcomes. The limitations may be associated with selection and participation effects, the absence of consumer out of pocket costs and blinding.*
- *Pragmatic randomised trials represent an alternative to more traditional clinical trials. They will involve randomisation but in a practical setting with less intensive follow-up than is typical in more traditional RCTs.*

Well-designed randomised studies that incorporate measures of compliance as either primary or secondary outcomes have the potential to assess the effectiveness of interventions intended to enhance compliance (such as alternative formulations) or the associations between certain consumer variables and compliance. However, the evidence to date is generally of low quality and inadequate for evaluating the effectiveness of interventions to improve compliance (NICE, 2009; Haynes, 2005). Variability in the methods used to measure compliance has been recognised as a constraint in comparing and interpreting both the magnitude of compliance and the evaluation of interventions to improve compliance.

In response to these concerns, a framework for planning and evaluating prospective studies on medication compliance and persistence has been published by Gwadry-Sridhar et al (2009). This framework is proposed to ensure that future compliance research will present and evaluate data more consistently.

B2.1 Randomised control trials

RCTs have been used mostly to measure the effects of different interventions on compliance in specific populations. In these circumstances, the RCT yields the strongest and most direct evidence on which to base a judgement on the effect of an intervention on compliance. However, the generalisability of such findings to clinical populations is often limited because RCTs are conducted in atypical settings with highly-selected populations and in strict accordance with research protocols.

Strengths

The key strength of the RCT is that the random assignment of participants provides the best means of mitigating the effects of known and unknown confounding factors. Randomisation, on average, is likely to achieve equivalence of study subjects across comparison groups with respect to all factors other than those under study. While known confounding factors can be controlled or adjusted for, randomisation should ensure that unknown factors are evenly distributed between comparison groups where the sample size is adequate.

A RCT could be designed to measure the appropriate duration of treatment for an acute or episodic indication. This is rarely possible using prescription refill data alone because, where dosage information is unavailable, the actual duration of therapy is unknown and limited by the length of the treatment supplied with each script. The potential for closer participant

follow-up in RCTs means it is possible to measure persistence more accurately over specific time periods.

RCTs that include a combination of outcome measures, such as self-report of medicine taking or electronic monitoring of dosing and timing, can provide more accurate assessments of compliance. These studies may also be able to assess reasons for discontinuation of or non-compliance to a prescribed medicine, thereby distinguishing appropriate from inappropriate non-compliance.

Limitations

RCTs are expensive, labour intensive and time consuming to perform.

When designing a RCT to assess interventions intended to improve compliance, it is important to consider selection effects and participation effects. *Selection effects* may arise when consumers recruited to RCTs are unrepresentative of consumers with the same disease in the general population in ways that may affect compliance. *Participation effects* occur when consumers who are involved in a trial, behave differently than they would if they received the same intervention as part of routine clinical care. Both of these factors may limit the degree to which the findings of RCTs are applicable in practice. The most probable direction of bias will be to overestimate the effects of interventions on compliance and its effects on health outcomes.

RCTs may not be suitable for evaluating differences in compliance between medicines where differences in formulations make it impossible to blind participants to the product that they receive. For example, a compliance study which compares treatments with different routes of administration is unlikely to be able to blind participants to their assigned treatment unless a complex double dummy design is used (e.g. consumers receive medicines by both routes with half of each active and half placebo). This approach may be useful when comparing two different medicines, e.g. comparing the current medicine which requires regular testing and dietary restrictions versus a new medicine which requires fewer tests and no dietary restriction.

RCT may also be unsuitable for measuring acceptance because it is unlikely that a trial participant would not accept a prescribed treatment after consenting to participate and are likely to be more highly motivated towards compliance. Likewise the use of RCTs in studies of adherence and persistence with chronic long-term therapies is limited by the length of the trial. For example, a six-month study comparing weekly versus six-monthly regimens for bisphosphonates would necessarily show 100% compliance for the six monthly regimes. Follow up of non-compliance and discontinuing consumers may be too short, incomplete or biased.

B2.2 Pragmatic randomised trials

One potential design for compliance trials is the pragmatic cluster randomised trial in which randomisation to a particular medicine occurs at the prescriber or medical practice level (Hotopf, 2002). The target population to receive alternative forms of a medicine could be identified without imposing limited exclusion criteria. Consumers would receive different medicine formulations that have the potential to improve compliance. For example, in assessing combination items, general practices could be randomly assigned either to a combination item or to the component medicines given separately. It would then be possible

to obtain follow-up information on compliance and longer-term outcomes by means of linkage with administrative datasets. Thus, PBS information collected during the follow-up period would enable persistence and adherence to be assessed. It would also be possible to assess the effect of any improvement in compliance on long-term health outcomes if consumer data were obtained from hospital morbidity and mortality records and linked with compliance data. This design brings challenges from a quality use of medicines perspective, where it is considered inappropriate to initiate treatment with a combination item where dose titration is more constrained and adverse events due to individual components are not easily detected. These difficulties can be overcome by admitting only those subjects who have previously been stabilised on separate component medicines.

Such a design has one major potential advantage over more traditional clinical RCTs: linkage with administrative datasets will substantially reduce the need to have ongoing contact with study participants. This would reduce the cost of the research and minimise participant (and possibly selection) effects. In Australia consent would still be required from participating practitioners and consumers for release of individual data from Medicare Australia and State and Territory based disease registers (Commonwealth of Australia, 2008).

B.3 Observational or Cohort Studies of Compliance

B3.1 Overview

Key Points

- *Observational studies of administrative data may be useful in evaluating compliance to classes of drugs in descriptive studies of medicine use.*
- *The scope of a compliance study using administrative claims data is dependent on the appropriateness of the data for answering questions on compliance.*
- *Prescription claims data are more suited to answering research questions on persistence and switching between medicines. They may address adherence where dosage is known and research designs account for gaps in treatment. They are less well suited to assessing acceptance of medicines unless they are linked to prescriber-generated data where acceptance has been documented.*
- *Studies of persistence should measure both intensity and duration of medicine use since the interrelationship between these two factors contributes to overall clinical effectiveness. For chronic conditions, gaps in treatment need to be taken into account.*
- *Non-randomised observational studies of compliance typically lack sufficient internal validity to confidently attribute differences in compliance to the effects of a specific intervention or medicine formulation. Associations may be inferred but direct causality is more difficult to establish.*
- *The use of large administrative datasets may produce statistically significant differences in compliance; however the practical or clinical significance of any such finding requires further justification/explanation.*

Observational studies of compliance can include the use of administrative data or medical records (chart review) with any of the following methods for measuring exposure:

- Prescriber data (prescriptions written);
- Prescription supply (pharmacy or funder databases); or

- Pill counts (recorded on treatment charts or consumer diaries).

The CMWG noted that any observational study using prescription supply data assumes that possession of a medicine is evidence of its use. Studies using prescriber data alone are further removed in that a consumer possessing a script is assumed to: (a) accept the treatment; (b) obtain the medicine; and (c) adhere with the prescriber's recommendation. These studies cannot provide definitive information about whether or not the drug is taken in accordance with the prescribed regimen.

The scope of any study using administrative data is dependent on the appropriateness of the data recorded for assessing compliance. Many administrative databases (such as the PBS database) do not record information on dose and frequency. Therefore it may not be possible to make valid inferences about levels of adherence from prescription refill data alone for many medicines. Medicines for which the recommended dose is one tablet daily or depot products are likely to be an exception. Therefore information from observational studies can be significantly enhanced by linking prescription refill datasets with other health datasets, e.g. medical record data such as MBS data and or data sourced directly from prescribers. This is technically possible in Australia, but access to health datasets is often constrained by privacy legislation (Commonwealth of Australia, 2008).

The assessment of the exposed time to medicines in studies of prescription refill data are generally based on the days of supply of the prescriptions dispensed. If these data are not specifically included in the dataset, then the accuracy of any assumptions relating to days of supply should be considered before drawing conclusions about compliance. For example, where prescriptions for chronic daily therapies are assumed to provide 30 days' supply, analysis of the distribution of days to refill for all prescriptions in the study population can be one way of justifying this assumption. Alternatively, the distribution may indicate that the majority of consumers are not refilling scripts after about 30 days, and an alternative explanation (other than non-compliance) for the extended use of scripts will need to be considered.

Strengths

Databases that are sufficiently large and capture a significant proportion of the population (such as the PBS dataset) provide considerable statistical power at a relatively low cost. They often hold consumer data that can be analysed over long periods of time, and they cover the use of rare medicines for rare diseases or very specific population sub-groups. Most importantly, they contain information on the actual supply of a medicine in routine clinical practice.

The fact that the analyses are retrospective also means that consumer outcomes are not affected by contact with researchers. This is a valuable strength in studies of compliance where consumers' behaviours are likely to be affected when they knowingly participate in a trial. Also when measurement is retrospective, the ethical issues raised by consumer randomisation to a particular treatment do not arise.

Limitations

The major limitation of all observational studies arises from consumers not being randomised to a particular medicine (intervention). In the absence of randomisation, the potential for unknown confounders to exist creates more uncertainty about the attribution of any

differences in compliance or health outcomes between the comparison groups to the intervention of interest. For example, if the intervention is the use of a combination product, and the comparison groups differ in the proportion of subjects with dementia (a confounding factor not measurable in the prescription data set), it would not be possible to determine whether differences in the prevalence of dementia among the comparison groups contributed to the observed difference in compliance. Thus inferring causality can be problematic in non-randomised studies using PBS claims data because an association between two variables does not alone establish a causal relationship. Non-compliance may occur for many other unmeasured reasons, as discussed in Part A of this report.

Confounding due to unmeasured differences between compliant and non-compliant cohorts may also affect the interpretation of non-randomised studies of compliance. The problem occurs when there are differences between the cohorts that affect the outcomes (also sometimes referred to as hidden bias). The result may be to inflate, attenuate or reverse the true effect of the intervention or variable of interest. For example, if the promotion of a medication creates a particular consumer profile in the mind of some prescribers, or if the treatment guidelines recommend the use of the medicine in a particular group of consumers, then medicines with comparable efficacy may be channelled into different groups of consumers with very different clinical outcomes regardless of treatment. The results can be misleading when the outcomes are attributed to the medicines, when instead they are more likely to reflect the prognoses of the particular groups treated.

Studies comparing compliance between combination medicines versus their alternative concomitant therapies are particularly prone to bias. This is because prescribers often stabilise consumers on the concomitant therapies before prescribing a combination product. This means that consumers who receive a combination product are unlikely to have adverse events and have a history of compliance with individual components.

These issues aside, the use of prescription refill as a surrogate measure of adherence and persistence is a rapidly expanding area of research. There is increasing evidence that these methods are highly correlated with other measures such as consumer self report surveys, direct observation and electronic medication monitors (Cook, 2005; Grymonpre, 2006; Kwon, 2003). Accordingly a detailed explanation on the methods and endpoints used in these studies is provided below.

B3.2 Specific methods applicable to retrospective observational studies using prescription refill data

Key points

- *This is a developing research area and methods are evolving to better support the inferences made in this field.*
- *Varying results can be obtained from the same data depending on the methods used and definitions applied to measure persistence and adherence.*
- *A study protocol should be developed and made publicly available prior to any data analysis in this area of retrospective research.*
- *Studies using prescription refill as a proxy for compliance must analyse data at the individual consumer level and follow dispensing in sequence over time.*
- *Measures of adherence and persistence should be analysed as continuous variables wherever possible, rather than as either ordinal or dichotomous variables. Reduction*

of available continuous variables into categorical variables usually leads to a loss of valuable information.

- *The distribution of days to refill of consecutive prescriptions per consumer for the medicines of interest provides a valid way of determining the appropriate permissible gap between prescriptions in any analysis.*
- *To account for continuous eligibility of participants in the study, it is necessary to account for loss to follow-up including death and other reasons. This is particularly important when studying populations with high rates of mortality and morbidity.*
- *Limiting analysis of persistence to new users' first episode may significantly underestimate persistence over a lifetime. Consumers on long-term therapies stop and restart medicines as they come to understand and modify their medicine regimens.*

Methods of measuring adherence

The MPR is the most commonly used method for calculating medication adherence (Peterson, 2007; Andrade, 2006; Vink, 2008). It is usually calculated by summing the number of days supplied for all but the last prescription, divided by the number of days between supply of the first and the last prescription. If the MPR is applied over periods of time of continuous supply, it can provide an estimate of adherence. When it is applied to periods of time without continuous exposure (i.e. gaps in treatment are not discounted), the MPR is subject to bias if the duration of gaps in therapy differ between groups. When used as a measure without regard to duration of treatment, it is sometimes called 'MPR flexible' or MPRF. The MPR can also be calculated using a defined time period such as year (MPRY). The MPR is easy to calculate but may obscure periods of oversupply and undersupply of medication.

A MPR greater than 1 or 100% (i.e. greater than full compliance) indicates that the consumer may be hyper-compliant, stockpiling or wasting medicine (Vink, 2008). It is not generally recommended that the MPR be based merely on the sum of the days supplied from all prescriptions filled during the study period, as this form of calculation ignores the potential for oversupply in some periods. Instead, it is recommended that decisions are made for each day in the follow-up period to be either covered or not covered (which limits the value of the MPR to the range 0.0-1.0). Overlaps should be adjudicated according to a clinically informed algorithm.

A second, and increasingly popular measure of adherence is the continuous measure of medication gaps (CMG). In certain medicines and diseases where continuous treatment is clinically important (such as glaucoma or HIV infection) this may be a more informing measure of adherence. The CMG is calculated by summing the number of days in the gaps between refills and dividing these by the number of days between the supply of the first and last refill. It can be calculated for a defined time period and used to estimate the percentage of days without medication during a specified time interval. This measure can be expressed as an adherence rate by subtracting this percentage from 100%.

Methods of measuring persistence

The simplest method for measuring persistence with medicines is the 'anniversary model'. A consumer is deemed persistent for one year if a prescription is filled in a specified time period around the anniversary of the index script. This method gives only a dichotomous measure of persistence versus non-persistence; it does not reflect continuous medicine use within the

year. Thus, for example, cessation of the medicine for six months in the middle of the 12-month period would be unrecognised.

A similar although slightly more complex method is the 'minimum refill model', where a consumer is considered persistent when a minimum number of prescriptions are dispensed during a set time period such as a year. This method also yields a dichotomous measure of persistence and requires justification for the minimum number of refills.

Discontinuation and/or continuation rates may also be used to assess persistence. Discontinuations are generally defined by an unacceptable gap between the dispensing of two prescriptions (or supplies). The estimated level of persistence with therapy (ELPT) calculates the percentage of subjects remaining on therapy at a given time. The data can be displayed on a persistence curve. The most common method of analysis is to construct a Kaplan-Meier life table with discontinuation considered from the event.

The proportion of days covered (PDC) is similar to the MPRY in that a specified time period (expressed in days) constitutes the denominator. However, the numerator is not the sum of the days of supply according to the prescriptions filled in the specified time period, but is adjusted for overlapping days or gaps in possession. The PDC can be analysed as a continuous variable or divided into categories as either an ordinal or a dichotomous variable, but it is desirable to retain the PDC as a continuous variable.

Study protocols and rules

Protocol rules refer to the initiation and discontinuation of subjects in a study, length of follow-up, switching between medicines for the same indication, days of supply, prescriptions dispensed and study timeframe. The application of these rules varies according to individual studies, and can affect the results obtained when quantifying adherence and persistence according to prescription refills. Varying results can even be obtained from the same data depending on the methods used and definitions applied to measure persistence and adherence (Caetano, 2006; Hudson, 2007).

There is also the potential for selective and biased reporting of results from multiple analyses of a large data set. For these reasons, study protocols should be specified and registered a priori. Pre specified study protocols that are accessible to the public, could be made a prerequisite for release of data from health data custodians. As a minimum these protocols should include: the aims of the study; details on the medications under study and their indications; the eligible population; the methods used to measure compliance and their applicability; definitions of initiation and cessation; duration of follow-up; and any statistical analysis that will be used. Pre specification of study rules will improve the quality of these studies and give greater confidence to the reported findings (Hemingway, 2009).

<u>Initiation</u>

Studies of compliance may need to be undertaken in new or continuing users depending on the research question. The greatest decline in persistence to chronic medicines occurs in the first few months of exposure, therefore accurate identification and classification of new users within retrospective cohorts is important to ensure comparable study populations are analysed. Initiation based on the first prescription presented in the study period may be a new user (known as an initiator) or possibly the first script dispensed following a break in refills (a re-starter). The definition of initiation should be pre-specified and justified by retrospectively confirming the absence of a script for a clinically meaningful time period preceding the start

of the study. In addition, consideration needs to be given to additional inclusion criteria such as the requirement for the dispensing of two consecutive prescriptions, which may be a surrogate indicator of the intended ongoing use of the medicine.

Discontinuation

Discontinuations are generally defined by gaps (days of non-supply) between two occasions of dispensing a drug, and may be referred to as the permissible gap for refilling prescriptions. The duration of the permissible gap should be such as to identify subjects who genuinely cease treatment, while allowing enough time for subjects who are continuing to refill their scripts. In Australia, this definition needs to allow for the annual cycle of safety net supply intervals, so that consumers who have stockpiled medicines each December are not incorrectly deemed to have discontinued each January. The researcher must also consider the accuracy of the recorded days of supply and the degree of clinical tolerance to short-term non-adherence with the medicines of interest. While 30 and 60 day gaps often form the basis of definitions of discontinuation, the use of these has been determined by convention rather than having been justified by the pharmacokinetic and pharmacodynamic attributes of the medicines under study (Cramer, 2007).

If the days of supply are recorded accurately in the dataset and they reflect the prescriber's intention, it may be reasonable to assume that they indicate the timeframe for appropriate adherence and persistence. In the absence of these data, the prescribed days of supply may be assumed on the basis of pack size and recommended dosing regimens. Alternatively, the actual numbers of days between refills of each repeat prescription in the dataset can be presented as a frequency distribution. Parameters determined by the distribution of the number of days to refill of all scripts can then be used to justify the appropriate permissible gap between scripts. If the permissible gap, as determined, reflects the number of days taken by the majority of subjects in the cohort to refill their prescriptions, the majority of those who continue treatment will be identified in any analysis of persistence. Assumptions around the length of permissible gap in treatment and the impact on compliance may also be tested by performing sensitivity analyses.

Where possible, the analysis should account for discontinuations that may reflect appropriate non-compliance, e.g. following an adverse event, admission to hospital, a prescriber-initiated change in treatment, or loss to follow-up through switching to alternative therapy. Datasets should be checked to ensure continuing eligibility of subjects and to account for deaths of subjects, particularly when studying populations with high rates of mortality and morbidity.

Duration of follow-up

The duration of follow-up should be justified and of sufficient duration to answer the compliance research question. Ideally, it will be the same for all subjects, or include statistical methods such as survival analysis to account for differing durations of follow-up. In studies of persistence, the data should reflect either length of continuous therapy to first cessation according to a specified gap in prescriptions, or length of therapy over a period indicative of likely lifetime use. Several studies (Hudson 2007; Roughead, 2009; Cramer, 2007b) have shown that subjects re-start therapy after breaks in treatment. This may vary with the disease treated. Limiting analysis of persistence to new users' first episode may significantly underestimate persistence over a lifetime where subjects on long-term therapies stop and re-start as their understanding of the treatment improves and they modify their regimen.

Switching

Researchers must specify how switching between medicines for the same indication will be managed in the analysis. The assessment of switching between medicines within the same therapeutic category is useful when evaluating persistence to long-term therapy. However, if the focus of the research is on the effect on persistence of a specific molecule or formulation, then switching may not be allowed and the subject is defined as non-persistent. The case for adopting either approach should be justified with reference to the research question.

Days of supply, prescriptions dispensed and study time frames.

The methods used to quantify exposure should be clearly explained. The explanation should describe how monthly supplies are incorporated into a specific timeframe, i.e. whether the number of days of supply from the last refill are included or truncated at the end of the study period. If there is potential for different numbers of days of supply or prescriptions across the study arms (e.g. when different formulations are being compared), the calculation should be designed to avoid bias in the assessment of exposure. In the case of chronic medicines, taken daily, any assumption that the quantity supplied (typically 28 or 30 tablets or capsules) equals the number of days of supply should be justified by providing the distribution of the number of days between refills for all consecutive scripts dispensed for each medicine studied.

B3.3 Interpreting compliance measures

Key Points

- *The distribution of indicators of compliance (e.g. MPR or PDC) for the individuals of a population is more informative than simply presenting a measure of central tendency (e.g. the median or the mean).*
- *The threshold at which compliance (versus non-compliance) is deemed to be clinically relevant requires justification.*

It is generally more informative to analyse continuous data than convert results of prescription analyses such as MPRs and PDC to arbitrarily determined categories or dichotomous values of compliance versus non-compliance. Presentation of the distribution of the results for all individuals is more informative with regard to the extent of adherence or persistence across the study populations. For example it is possible to differentiate between a few totally non-compliant subjects and a large number of partially compliant subjects, despite both populations having similar mean MPR's.

For many medicines, it is assumed that the consumption of at least 80% of the intended dose represents compliance, because taking four-fifths of the intended dose is considered unlikely to compromise clinical outcomes. However, as discussed in Part A2.5, clinical evidence to support this figure is available for only very few medicines. One recognised exception is that consumers with HIV infection need to take more than 95% of protease inhibitor medicines to prevent the development of HIV antibodies (Grossberg, 2007). As research in this area progresses, clinically meaningful thresholds of compliance for other medicines need to be determined.

B3.4 Statistical methods to control or adjust for bias in non-randomised observational studies of compliance

Broadly, comparative studies of factors hypothesised to influence compliance can be weakened by three types of bias:

- Measurement (or information) bias;
- Selection bias; and
- Confounding.

Measurement bias may occur when the factors being studied (i.e. the determinants) and/or the indicators of agreement, adherence or persistence are measured or classified inconsistently.

Selection bias may occur when procedures used to select subjects lead to a situation in which entry into the study is itself associated with a factor that predicts increased or decreased compliance. For example, the use of volunteers for a study of compliance could lead to selection bias because a group of volunteers for a pharmacy study is likely to contain a high proportion of people who have a conscientious attitude towards medication use. In this specific situation, the strength of the association between the determinants being studied and compliance will be spuriously increased (positive bias). It is also possible to envisage specific situations where the strength of the association will be spuriously decreased (negative bias).

Confounding may occur where there are baseline differences in the distribution of determinants of compliance (other than the determinants of interest in the study) among the groups of subjects being compared. These determinants are known as confounders. Confounders may cause a positive or a negative bias, depending on the nature of their effect and the characteristics of their distribution in the comparison groups. As discussed in Part A of this report, many of the factors that influence compliance (determinants) are not easily identified or quantified.

Measurement and selection bias arise in the design and execution of a study and when adjustment in the analysis is not possible. In contrast, adjustment for known confounders is possible if data on them are available. If potential confounders are identified but data on them are unavailable, the researcher should acknowledge their potential effect and, if possible, describe the direction of the bias that they are likely to cause. Random allocation of subjects to comparison groups may overcome the potential bias arising from unrecognised or unmeasurable confounders.

Several methods can be used to adjust for identified confounders on which the researcher has collected data. These are as follows.

Stratification

Subjects are grouped into categories, or strata, of each (potential) confounding variable. For example, if age and sex are potential confounders, subjects could be grouped into appropriate age-sex strata. Results can be analysed by stratum, and the stratum-specific estimates can be combined using a variety of techniques, thus controlling for confounding. Stratum-specific data can also be used in subgroup analysis. While stratification is simple and intuitive, the number of confounding variables that can be managed simultaneously by stratification is usually limited by the sample size.

Regression techniques

A variety of regression techniques can be used to adjust for confounding in different situations.

- Multiple regression is used to examine the relationship between two or more determinants and a dependent variable such as compliance, where compliance is measured on a continuous scale. It involves fitting a regression model – usually an equation for a linear model – to the observed data. The coefficients of the individual terms for the determinants within the equation can be used to estimate the magnitude of their effect on compliance, and whether or not their effect is statistically significant.
- Logistic regression is an analogous method that is used to examine the relationship between two or more determinants and a dependent variable that is binary or dichotomous, e.g. compliant or non-compliant. Logistic regression is of limited utility in studying factors affecting compliance because compliance is not usually considered to be dichotomous.
- Cox proportional-hazards regression is used to analyse the effect of several determinants on the length of time taken to reach a particular outcome. For example, it can be used to examine the factors affecting the length of time over which individuals persist with medications. The dependent variable in the regression equation could be the amount of time until a consumer ceases to be compliant.

Propensity Scores and Instrumental Variables

The use of methods such as propensity scores and instrumental variable analyses may assist in overcoming confounding, but their application in compliance studies to date has been limited. Kaplan-Meier analyses are most commonly used. Competing risk methods may be required in situations where another significant event (e.g. death, disease progression) would preclude the compliance event (e.g. switching, cessation) of interest from occurring.

The instrumental variables method is taken from econometrics. The instrumental variable is correlated with exposure and does not have an independent effect on the outcome for the subject. Studies using the instrumental variable approach should employ standard econometric tests to ensure the validity of the instrument employed. The use of inappropriate instruments can produce biased or misleading results (Baser, 2009).

B4 Administrative Datasets and Compliance Research

B4.1 Studies of Prescription refill from Australian administrative datasets.

Key Points

- *The PBS and Repatriation PBS (RPBS) datasets provide comprehensive Australian prescription data for the majority of prescribed medicines. However, sufficiently detailed data on prescriptions priced under the general PBS co-payment threshold are not yet collected by Medicare Australia.*
- *Methods to measure compliance based on prescription refill data have largely been developed in the USA and other countries where administrative datasets often include linked prescriber and health-service utilisation data.*
- *The potential to perform studies of compliance and their relevance to treatment outcomes is limited by the absence from the PBS and RPBS datasets of data on medicine doses, number of days of supply and indications.*

- *The ability to adjust or control for confounding in observational studies of compliance is limited by the lack of access to linked health-service data in Australia.*

Medicare Australia PBS and RPBS Data Issues

In Australia PBS and RPBS prescription claims data capture most of the medicine use throughout Australia, particularly the use of medicines that are prescribed for long-term chronic conditions. However, the datasets have some limitations. The most important limitation is the absence of data on the dosage prescribed (as distinct from the strength prescribed), the frequency of administration and the intended duration (as distinct from the quantity supplied). Most of the techniques for estimating compliance using prescription refill data described in the literature have been developed in datasets that include data on the numbers of days of supply and doses. The availability of data on these variables enables more accurate assessments of the level of exposure to each medicine. The absence of such information from Australian datasets limits the scope of compliance studies to medicines that are typically prescribed with stable dosing regimens (e.g. medicines with a fixed daily dose and a 28-day or 30-day supply per script).

Prescription data on PBS and RPBS listed medicines priced under the general co-payment threshold are not currently collected for the Commonwealth by Medicare Australia where consumers are not concession card holders. Research studies must recognise that collecting and analysing data for concession card holders only, may not provide results that are applicable to the whole population. Some progress has been made towards collecting data at the pharmacy level on prescriptions for consumers who are not concession card holders, and adding these data to the main PBS dataset (DoHA, 2005). The availability of these data will substantially enhance pharmaco-epidemiological studies in Australia, including studies of the effects of compliance on health outcomes.

The PBS and RPBS include a 'safety net' which provides for general category consumers (i.e. those who are not concession card holders) to receive medicines with the same co-payment as that made by concession card holders if their total co-payments reach a threshold amount in any calendar year. Concession card holders have an analogous threshold above which their co-payments are waived altogether. The safety net creates specific anomalies in PBS data because reimbursed prescriptions for some general category consumers may appear in the PBS dataset at certain times of the year but disappear at other times. While the precise times when consumers appear in and disappear from the PBS dataset depend on individual factors, they are most likely to disappear towards the start of any calendar year and reappear in the middle or later half of the year.

The PBS dataset is not linked to data on deaths and therefore does not include dates of death of individuals who have received prescriptions. Cessation of medications due to death could be taken into account if dates of death were available, and in their absence cessation of medications is likely to be overestimated particularly for medicines prescribed to the very elderly. Similarly, those consumers who are admitted to hospital for extended periods will also disappear from the PBS dataset.

Researchers can apply to Medicare Australia for a sample of de-identified PBS data for purposes that are in the interests of the health of Australians. The Medicare Australia website provides information on how to apply for such data –
http://www.medicareaustralia.gov.au/about/stats/navigate.jsp

Data Linkage

Data linkage involves, for example, linking confidential medical records from visits by individuals to doctors and hospitals so as to follow their progress through the health system (for example, from the doctor's office to the hospital bed and back again). Data linkage can therefore be a valuable research tool.

However, as this type of research involves the use of personal information, stringent legislative requirements ensure that privacy is protected. In principle, it is possible to establish privacy-protecting data linkage methods to link the PBS data to other datasets such as MBS data and State and Territory hospital records.

The Department of Health and Ageing in collaboration with a range of Commonwealth and jurisdiction stakeholders is currently engaged in data linkage and policy work. For example, linkage of PBS data is currently achieved:

- Internally by the Commonwealth Departments of Health and Ageing, Veterans' Affairs and Medicare Australia;
- Through linkage with State and Territory datasets; and
- By other research groups where prior participant consent has been obtained (e.g. the Women's Longitudinal Health Study).

B4.2 Examples of compliance studies in Australia using administrative data sets

Compliance studies have been undertaken using health data from the Department of Veterans' Affairs. The advantages of this dataset are as follows: it provides a complete coverage of the veteran population using RPBS medicines; all prescriptions supplied to veteran population are collected by Medicare Australia ('complete coverage'); and the dataset incorporates demographic data, including date of death. Therefore censoring for death and adjustment for confounders (such as age, gender, residential aged-care status, co-morbidities and socioeconomic index based on postcode of residence) can be achieved readily. One limitation of the dataset is that the veteran population has an older age distribution than the general population - most veterans are aged 55-plus years. Therefore there is limited generalisability. Published studies from the dataset have assessed compliance to bisphosphonates (Roughead, 2009c), cardiovascular medicines in veterans hospitalised for ischaemic heart disease (Roughead, 2009b), heart failure medicines and their impact on delaying hospitalization (Roughead, 2009a). In addition measuring compliance has also been important in other studies measuring the potential for adverse events (Roughead, 2008) and impact of multiple brands (Kalisch, 2007). Specific feature of the methodologies developed include the importance of analysing refill data for gaps in therapy, variability of time to refill in the study population and impact this has on assumptions of 'initiation of therapy', and measuring the extent of adherence.

Compliance studies have also been undertaken using a randomly selected 10% sample of PBS claims data provided by Medicare Australia. Simons et al (2008) undertook a longitudinal analysis using this dataset for the period from January 2004 to December 2006. Data were extracted on subjects who initiated (defined as no anti-hypertensive medications

dispensed in the previous six months) on an angiotensin II receptor antagonist (A2RA), an angiotensin converting enzyme (ACE) inhibitor, and/or a calcium channel blocker (CCB). The main outcome measures were the proportion failing to fill a second prescription, the median persistence time, persistence with medication over 33 months, and the median MPR.

Further studies used the same PBS claims dataset to examine several other aspects of compliance, as follows: time to re-start anti-hypertensive therapy after a six-month treatment gap, time to 'inferred' death, persistence to add-on treatment and persistence to specific anti-hypertensive medicine combinations (Ortiz and Calcino, 2009a -2009d).

The studies that used Department of Veterans' Affairs data, described above provide important information on the patterns of use of selected medicines in Australia, but they were not designed to compare compliance to specific products within the same therapeutic class. The study of anti-hypertensive medicines by Simons et al (2008) did compare individual products for persistence and adherence, and identified some interesting differences on the number of days to refill prescriptions among different products and pack sizes. The design of this study allowed for switching between classes of antihypertensives (i.e. between CCB, A2RA or ACE inhibitors) and censoring for persistence was defined as a three-month period without refilling a script (two month gap).

B4.3 Applicability of overseas studies of compliance

Key Points

- *Descriptive studies which measure the level of compliance in different populations are unlikely to be directly transferable between countries with different health-care systems and methods of funding pharmaceuticals.*
- *Comparative studies of compliance are likely to be informative when interpreted in light of the characteristics of the health care settings within which they were done.*
- *Ideally, evidence on comparative compliance to medicines should be based on data collected in the Australian health care setting. Overseas studies may provide complementary evidence to some decisions.*

In some circumstances, it may be reasonable to consider results from comparative studies of compliance to medicines from other countries when evidence for a particular medicine is not available in Australia. However, the health care setting and the variables measured should be examined in detail to assess their applicability to the Australia population for whom the treatment is intended.

The results of overseas studies of compliance may also be useful when considered in conjunction with Australian findings. Indeed, overseas studies may reinforce the results of Australian studies if their findings are in the same direction, particularly where Australian studies may have been subject to biases that overseas studies have apparently been able to control because of the availability of data on potential confounding variables.

B5 Measuring the Effect of Compliance on Health Outcomes

Key points

- *Ideally studies should include both measures of compliance and health outcomes.*

- *The association between compliance and a medicine (claiming superior compliance) must be established before any effect on clinical outcomes can be directly attributed to that particular form of medicine.*
- *The quality of the measurement of compliance affects the estimate of the association between compliance and treatment or health outcomes.*

The primary interest of the PBAC, and indeed any funder of health interventions intended to improve compliance, is in the attribution of health outcomes to compliance at the population level and/or in sub-groups of the population. In order to evaluate such interventions consistently with other PBAC's processes for considering submissions for PBS listing, methods for linking changes in compliance to longer term health outcomes must be established.

One possible approach would be to establish a relationship between compliance and an intermediate outcome where good evidence exists to show that the intermediate outcome predicts longer-term health outcomes. For example, in the evaluation of an intervention to promote compliance to a medicine that prevents cardiovascular disease by reducing blood pressure, changes in blood pressure could be a potential intermediate outcome; abundant evidence shows that lowering blood pressure leads to improved longer-term outcomes such as reductions in the occurrence myocardial infarction and stroke. To evaluate combination therapies, it may be possible to use existing evidence on the efficacy of individual therapies to estimate the efficacy of a combination therapy and hence quantify the improvement in longer-term benefits that may result from improvements in compliance. A similar approach could be used to evaluate long-acting formulations where the clinical benefits of the short-acting therapy could inform quantification of the health benefits of improved compliance. This approach depends on modelling and so should not be seen as a substitute for collecting more direct evidence where possible. If direct evidence cannot be obtained, modelling does enable systematic estimation of the potential benefits using assumptions based on the best available evidence.

Long-term follow-up studies have great value in determining whether a relationship exists between compliance and health outcomes. Such studies may either be pragmatic randomised trials (see Part B2.3) or, if confounding effects can be confidently minimised, cohort studies and case control studies. It is important to recognise that Australia is an excellent site for such studies because of the existence of relatively consistent ongoing population-wide data collections on key health outcomes. While collecting long-term information on large numbers of consumers to assess compliance would be expensive, this research can directly inform decision making on therapies that constitute an increasing proportion of the PBS and the overall health budget.

B6 Measuring the Cost Effectiveness of Interventions to Improve Compliance

Key points

- *For a compliance-enhancing intervention such as a change in medicines or formulation to be cost effective from the perspective of the funder, an economic evaluation should demonstrate that:*
  - *The intervention (the alternative or substituted medicine) improves compliance in a way that can be linked to health gain;*
  - *The cost of the intervention must be such that it is cost effective;*

- *Where possible, results should be expressed using measures that are widely accepted in economic evaluations, such as quality-adjusted life years (QALYs).*
- *The duration of observation in economic evaluations should be sufficient to demonstrate full or partial compliance and reflect the cyclical use of chronic medicines.*
- *Where the duration of observation is sufficiently meaningful, modelling methods can be employed appropriately to estimate long term effects of compliance.*

Several reviews (cited in Part A2.5) have shown that non-compliance is generally associated with reduced efficacy. Despite this, a review by NICE (2009) found that the relationship between non-adherence and cost-effectiveness was less clear. Eight studies found that costs increased as adherence decreased and six studies reported the opposite trend. The differences did not appear to be specific to a disease area or method of measuring compliance and health outcomes. Changes in compliance affect both the numerator and the denominator of the incremental cost effectiveness ratio (ICER) so the effect on the ICER is not always predictable.

Where compliance affects survival, quality of life and resource usage, medicines with the potential to be cost-effective through improving compliance should be evaluated in well designed studies that measure both compliance and health outcomes. Quantification of improvements in compliance leading to positive health outcomes is more useful than quantification of the effect of decreases in compliance leading to negative health outcomes.

The integration of compliance in pharmaco-economic evaluations is a major challenge. Decisions on the cost-effectiveness of medicines claimed to improve compliance are inevitably affected by factors which vary over time: for example varying states of consumer compliance and changes in the costs of new formulations and comparators. Such changes alter the basis of estimates of cost effectiveness, and are likely to lead to reconsideration of the relative value of a formulation that has been put forward as giving a compliance advantage. Given the dynamic state of the pharmaceutical market and hence the pricing of different interventions or formulations, their relative value may have to be re-assessed repeatedly over time against alternative strategies designed to improve compliance.

Part C: Comparing Compliance with Combination Items versus Alternative Therapies

C1 Introduction and Framework

The purpose of Part C is to provide guidance for the assessment of evidence on compliance to combination items in comparison with the most likely alternative therapy. Subsection 101(4AC*)* of the *National Health Act* applies only to single-branded combination items, i.e. those included now or in the future in the PBS Combination Items List (CIL) and these items are not included in either the F1 or F2 formulary. The current CIL is given in Appendix 2. The guidance provided here does not apply to the assessment of evidence for enhanced compliance to single-component medicines in formulations that offer alternative modes of administration or longer duration of effect.

Under Subsection 101(4AC) of the *Act,* the PBAC is required to consider and advise the Minister if a therapy involving a combination item provides a significant increase in compliance for some consumers. Subsection 99ACC(4) of the *Act* states that

> "if the PBAC gives advice to the Minister under subsection 101(4AC) in relation to the combination item, then, in working out the new price of the single brand of the combination item, the Minister may have regard to that advice in considering the extent (if any) to which to reduce the existing agreed price."(*National Health Act,* p255)

Neither subsection makes provision for a price increase over the current list price of a single brand combination item, but allow for a single-branded combination item to avoid the flow on of statutory price reductions occurring in the individual components drugs, (in part or in full). All claims for price variations based on claims of enhanced compliance to products other than combination items, must demonstrate improved effectiveness and cost-effectiveness in accordance with the existing Submission Guidelines (DoHA, 2008).

Table 3 provides a framework for the evaluation of evidence on compliance to combination items compared with alternative therapies.

Table 3: Framework for assessing evidence to support claims of increased compliance to combination items

Question	Potential sources of evidence	Reference to this Report
1. What is currently known about the level of compliance to this medicine(s)? • What is the current level of compliance (i.e. acceptance, adherence and persistence)?	Structured literature review, systematic review. Current persistence in PBS administrative data and prescription claims data. Other studies of compliance, including validated self report, direct observation, pill counts, prescription refills, electronic medicine monitoring.	Part B
2. What is known about factors that affect compliance to this medicine? • Individual consumer behaviours and caregiver behaviours. • Disease characteristics. • Characteristics of the practitioner or prescriber. • Health system factors. • Characteristics of the medicine, the formulation and the regimen. Consider the extent to which each factor may contribute to non-compliance (e.g. consumer factors 10%, system factors 10%, and medicine formulation factors 50%)	Identify potential factors that affect the use of this medicine. • Qualitative and quantitative studies of factors affecting compliance • Cross-sectional surveys of reasons for non-compliance • Self report surveys in randomised trials that include reasons for non-compliance	Part A3
3. How, and to what extent, can the combination item affect the factors contributing to non-compliance in the population of interest?	• Published studies • Plausible explanation • Survey of prescribers • Survey of consumers	Part A
4. Is there evidence available to show that there are measured differences in compliance and, if so, that these are associated with use of the combination item versus its alternative therapies?	Comparative studies of compliance to the combination item versus alternative therapies e.g. observational studies or pragmatic trials.	Parts B2 and B3
5. Is any measured difference in compliance sufficient to affect health outcomes, i.e. is it clinically significant? How critical is compliance to achieving the desired health outcomes for the medicine prescribed?	Studies of the effect of compliance on health outcomes (preferably from studies designed to measure compliance that also includes measures of health outcomes). • Pharmacokinetic studies • Dose-response studies including data on duration of medicine usage Outcomes data from RCTs	Part B5

Table 3: Framework for assessing evidence to support claims of increased compliance to combination items

Question	Potential sources of evidence	Reference to this Report
6. What is the effect on PBS expenditure of retaining the price of the combination item when the price of one of its component medicines undergoes a statutory price reduction, in comparison with applying these price reductions to the combination item?	• Estimate of projected PBS utilisation at current listed price • Estimate of projected PBS utilisation following price reductions applied from component medicines	Part C5

C2 The Population and Health-Care Environment

This Part should be read in conjunction with Points 1, 2 and 3 of Table 3.

Key Point

- *Interpretation of any comparative study of compliance must consider the health-care environment in which a medicine is prescribed and administered including:*
  - *the specific disease to be treated or prevented;*
  - *the pharmacological properties of the medicine itself;*
  - *optimal level of consumer compliance; and*
  - *the multiplicity of medicines and other treatments accessed.*

As discussed in Part A3, a body of literature exists on factors affecting compliance in specific health-care environments. A comprehensive review of the literature relevant to the medicines of interest and the population being treated is likely to help in determining the issues that might affect the assessment of compliance.

The following questions about the population are germane:

1. What are the characteristics of the population in which this combination item is likely to be used?
2. What is known about the base level of compliance to the components of the combination item (acceptance, adherence and persistence) in this population prior to the introduction of the combination item?
3. If non-compliance is a problem, what reasons are commonly given by consumers for non-compliance, and to what extent will switching to the combination item address these reasons?
4. Do different subgroups of the population have different levels of compliance and why?

The fourth question is important because an unequal distribution of subgroups that have different compliance characteristics within study cohorts could bias the results of non-randomised comparative compliance studies.

Knowledge of other current or planned compliance-related interventions in the population of interest is essential in assessing the results of comparative studies on compliance to different products. For example, the existence of promotional or reminder systems for only one of the alternatives under comparison in a study could bias compliance results. In addition, differences in the marketing of the compared alternatives might influence prescribers' and consumers' choices.

C3 Evidence on Compliance with Combination Items versus Alternative Therapies

This Part should be read in conjunction with Point 4 in Table 3.

C3.1 The Comparator

Key Points

- *A comparative study of the combination items and the most likely alternative therapies is necessary to provide evidence of any difference in compliance that is likely to be attributed to therapy involving the combination item.*
- *Selection of the appropriate comparator should accord with the principles that the PBAC applies to all submissions for PBS listing of medicines, even though the context of the decision may be reversed, i.e. considering the potential removal of an item rather than considering the potential addition of an item.*
- *For applications seeking consideration under Subsection 101(4AC), the comparison should be against the alternative therapy that prescribers would most use in practice if the combination item were removed from the PBS.*

As one consequence of PBS Reforms, the assessment of compliance has become an issue in its own right under Subsection 101(4AC) of the *National Health Act.* Inevitably, this requires the provision of evidence to enable a comparison to be made against the alternative therapies.

The first step is to identify and define the alternative therapies, considering that these may change over time. The alternative therapies relevant at the time of listing may not be relevant when the Minister subsequently considers the extent of any price reductions to the single-branded combination item. The component drugs of the single-branded combination may not be available on the PBS, or alternatively other therapies may become relevant comparators in the meantime. For example, competing combination medicines might subsequently be listed on a cost-minimisation basis compared with the earlier combination medicine (see Product Type 1.2 in Guidelines for preparing submissions to the PBAC, Version 4.3, DoHA, 2008).

The selection of the most relevant alternative therapy should be in keeping with the principles already established for determining the main comparator in a submission to the PBAC. However, the PBAC consideration should also include an assessment of the consequences of a possible de-listing of the combination item, in the event that a price agreement cannot be reached between the Government and the sponsor. In these circumstances, the most appropriate comparator is the therapy or therapies that prescribers would most use in practice if the combination item were removed from the PBS.

If this approach is accepted as the basis for determining the most appropriate alternative therapy in the context of Subsection 101(4AC), then an understanding of how prescribing decisions are made becomes important. Once therapy has been started with a combination item and subsequently it is removed from the PBS, the prescriber's likely response should be considered. It is possible that prescribers could return to the component medicines given concomitantly. However, if a similar combination medicine which has been accepted as equi-effective is available, it seems more likely that prescribers would switch to it, especially if they expect that improved compliance would be maintained. In these circumstances, a compliance advantage for a combination item over its single component items that are the subject of future price reductions is irrelevant, as these component items no longer represent the most relevant alternative therapies.

Again, in keeping with the principles already established for submissions to the PBAC, there may also be circumstances where a comparison should be presented against more than one alternative therapy.

C3.2 Published comparative studies of combination medicines

Key Points

- *The literature provides limited guidance on the research methods that specifically address compliance to fixed-dose combination medicines versus their alternative concomitant therapies.*
- *In situations where several medicines are used to treat one disease (one or more of which may be a fixed combination product), measurement of the value of the individual medicines to health outcomes, using prescription refill data, may be problematic.*
- *Most comparative studies of compliance to combination medicines have been conducted in the USA, often using prescription data linked to prescriber and other health service information.*

As noted in Part C1, little published literature exists on the methods specific to assessment of compliance to combination products versus their alternative concomitant therapies.

Several publications describe the methods of measuring two components of compliance (adherence and persistence) using retrospective prescription refill data (Caetano, 2006; Andrade, 2006; Peterson, 2007; Vink, 2008). These publications provide broad guidance on the commonly-used methods and metrics. However, the methods have been primarily developed using overseas datasets, and focus on measuring adherence and persistence to an individual medicine or class of medicines. When comparing compliance to two forms of a medicine, additional problems emerge in establishing meaningful measures of prescription refills. These problems are examined and discussed in greater detail in Part C3.3.

Measuring adherence to multiple related medicines in non-trial settings where people take several medications to treat a disease or condition is difficult. A recent publication by Chouhdry et al (2009) addresses some of the issues that arise when measuring adherence to multiple related medicines using prescription refill data. Commonly, consumers with chronic conditions such as diabetes or hypertension switch between classes of drugs and receive multiple medications to treat their disease. Measuring compliance to one medicine or class of medicines may underestimate compliance for some of these consumers. They also identified

the different estimates of adherence obtained when applying different analysis rules such as varying length of follow-up, permissible gaps and dichotomous values of adherence (MPR>80%) to the same data. To date there is little guidance to address the problems associated with measuring persistence to multiple related medicines including the components of combination medicines.

The difficulties associated with analysis have also been highlighted by NICE. NICE (2009, p236) critiqued a meta-analysis by Bangalore (2007) drawing attention to methodological concerns that could have affected the findings of this meta-analysis. This meta-analysis of nine studies compared compliance to combination products with compliance to separate component medicines. Of these nine studies, only three reported efficacy outcomes. The findings of this review suggest that combination medicines reduce the risk of non-compliance and should be considered in consumers with chronic conditions such as hypertension. NICE considered there was considerable uncertainty in this conclusion.

Published studies of compliance with combination medicines compared to the component medicines taken concomitantly have conflicting results (Legorretta, 2009; Dickson, 2008; Patel, 2008). Some studies indicate that compliance is improved when a combination medicine is prescribed instead of its components, particularly in the chronic management of hypertension. In contrast, Melikian et al (2002) measured adherence to oral anti-diabetic medicines finding no significant difference in the adherence measures among newly-treated study subjects receiving monotherapy, concomitant medicines or combination medicines. However, previously-treated study subjects did show better adherence to combination medicines (Melikian et al, 2002). This difference in measured effect between new users and experienced users was highlighted in B3.2.

NICE (2009) also searched for evidence that changes in dosing regimen improve compliance. No convincing evidence was found to show that changes in formulations improved adherence, leading to the suggestion that changes should only be considered as a response to individual consumer needs.

C3.3 Observational studies of prescription refills comparing compliance between combinations items and component medicines taken concomitantly

Key Points

- *Observational prescription refill studies represent an emerging area of research, and the exploration of different methods of analysis is warranted.*
- *Multiple measures are necessary to interpret compliance reported from prescription refill studies, including compliance to individual components of a combination medicine, compliance to class of drug, and compliance to therapeutically equivalent drugs.*
- *It is important to examine the analytical methods used for taking account of the active components of medicines and incremental benefit relative to number of prescriptions.*
- *Unintended outcomes such as hyper-compliance may occur when switching from single-component to fixed-combination medicines.*

Selection bias and confounding

Observational studies that compare combination items to the components taken concomitantly are particularly prone to selection bias and confounding because of the

existence of known and unknown factors that influence prescribers' and consumers' use of the various products. For example, prescribers may chose a combination item in preference to the individual components for consumers who have more stable disease and are more adherent generally. In this case, should better health outcomes be found in this group taking the combination item, the improved compliance and health benefit cannot necessarily be attributed to the combination item itself. There may be many other valid clinical reasons for prescribing one product instead of another for the same indication. For example, unstable or more critically ill consumers may be prescribed individual components to allow for more flexible dosing. This bias could result in better compliance (if the consumer is well cared for) but could still be associated with poorer health outcomes.

Prior exposure is another known confounder that contributes to bias. Best practice or clinical guidelines often direct prescribers to stabilise consumers on the concomitant separate medicines before changing to a combination product. This very practice may bias compliance studies, as those starting on a combination product are more likely to be users with prior exposure to the medicines and less likely to stop because of adverse events or intolerance to any component.

Some, but not all, of the known factors that may cause biases can be measured and adjusted for either by stratification or by the use of other statistical methods. Nevertheless, adjustment cannot be made for unknown (and therefore unmeasured) sources of bias, leading to uncertainty around the relationship between measured compliance differences, improvements in health outcomes and the use of combination items.

Compliance to molecule versus a therapeutic class of medicines

An understanding of the therapeutic options, including alternative medicines of the same class, alternative options in different classes with similar therapeutic benefits and the use of individual components, is necessary for studies attempting to show an effect attributed to a combination item. Consumers treated for diseases such as diabetes and coronary artery disease often receive multiple medicines within and across therapeutic classes. Defining a single comparator to a combination product may be difficult because these consumers switch, add and subtract multiple medicines within and across classes, often for good therapeutic reasons. Therefore, when measuring and defining persistence with a combination item versus its component parts, it is important to determine the appropriateness of switching between clinically indicated therapies. This raises the question of whether participants in the respective cohorts can switch to single-component medicines in the same class, and *vice versa*. Non-persistence with a specific product may not reflect non-persistence to a therapeutically appropriate regimen.

C3.3.3 Assigning values to prescription counts

The potential for measurement biases arise in comparisons of the numbers of prescriptions between cohorts of consumers taking combination items versus those taking single-component medicines. The way in which multiple prescriptions are counted and defined as co-administration can bias measures of medication possession relative to counts of single prescriptions for combination items.

Further, when the count of multiple prescriptions for individual components is compared to the count of single prescriptions for a combination item, it is important to define the value

assigned to prescription count with reference to the clinical benefits obtained. For example, in a study comparing compliance to Vytorin (a fixed combination of ezetimibe and simvastatin) with compliance to concomitant ezetimibe and simvastatin, it is important to consider how compliance to simvastatin or ezetimibe alone has been valued in the sum of scripts and interpreted in the results. Does compliance to simvastatin alone represent only half of the value of compliance to Vytorin? An analysis that halves the value of compliance for taking simvastatin alone may not be clinically appropriate. This is because consumers who have ceased ezetimibe and continue on a higher dose of simvastatin may achieve a better clinical response than those who continue to take both ezetimibe and simvastatin concomitantly or as a combination in the form of Vytorin - both of which are considered to have double the prescriptions counted in the MPR.

Unintended outcomes associated with fixed dose combination products

Unintended outcomes should be considered and accounted for when interpreting the results of compliance studies based on prescription refills. Higher counts of prescriptions dispensed do not always reflect a beneficial increase in compliance. Evidence from PBS data suggests that a small proportion of consumers who initiate combination products become hyper-compliant due to double dosing from two products containing the same medicines, i.e. they do not cease one or both of the component medicines when initiating a combination product containing the same active molecules (M Robinson, DUSC Secretariat, pers. com). Conversely, wastage and non-adherence may increase among consumers who experience side-effects from only one component of a combination product compared to those on the component medicines, i.e. initiation of a combination product may lead to a doubling of the wastage if the consumer experiences an adverse event related to only one active molecule in a combination item.

C3.4 Other possible designs for comparative studies of compliance to fixed-dose combination medicines

Key point

- *Some research questions may be better answered using prospective or pragmatic randomised trials.*

As presented in Part B of this report there are a variety of study designs available to assess or measure compliance that could be applied to comparative studies of fixed combination products and their comparators such as:

- Randomised trials, in which subjects are randomly assigned to receive two or more products with differences that are hypothesised to affect compliance, and where compliance with the product affects the outcomes.
- Prospective observational studies, which compare compliance rates and ideally health outcomes in subjects who variously receive and do not receive a combination product.
- Pragmatic randomised trials (refer to Part B2.3)

The ability to capture use of medicines over extended periods relatively cheaply through administrative datasets has led to increasing reliance on retrospective observational study designs to measure compliance. The CMWG was concerned that other potential designs are not discounted when considering evidence in this area. The use of alternative well designed studies that incorporate self report or clinician input may provide more comprehensive information that is not obtainable through prescription refill and administrative datasets.

Alternatively the use of prospective designs that incorporate some degree of randomisation of subjects may provide results that are less uncertain in regard to hidden biases and enable studies of medicines that are not administered continuously or uniformly.

C4 Interpretation and Extrapolation of Compliance Differences

This Part should be read in conjunction with Point 5 in Table 3.

Key points

- *Any measured difference in compliance must be linked (ideally in the same study) to the effects on primary, secondary or surrogate health outcomes and consumer-relevant outcomes.*
- *It is important to consider when it is reasonable to extrapolate the effect on compliance measured over a short time frame to long-term therapy. The use of modelling is unlikely to be appropriate in many situations.*
- *It is difficult to attribute a clinically meaningful health outcome to an improvement in compliance to one combination item that is only one part of a total treatment plan including multiple other therapies.*

To determine whether a change in compliance is clinically meaningful, an interpretation is required for each of the following three points: (i) attributing a change in compliance to a change in health outcome; (ii) whether or not the change in the health outcome is clinically significant; and (iii) whether or not the change in the health outcome is meaningful to the consumer.

For any claim of improved outcomes to be considered attributable to the combination product, a valid difference in compliance must first be established between the comparative medicines. An assessment of associated issues, such as the distribution of compliance in the study population, hyper-compliance and wastage, should also be considered. For example, if the level of compliance across a population improved by 10% for everyone who was taking a fixed combination product, a change in a surrogate measure of a health outcome may only be detectable among consumers whose baseline compliance level was marginally (<10%) sub-therapeutic. The improved compliance in this portion of the population would lead to the intake of a therapeutic dose and a likely improvement in surrogate measure of health outcome. In contrast, consumers whose baseline compliance level was markedly sub-therapeutic continue to take a sub-therapeutic dose despite the 10% improvement in compliance. The same applies to consumers whose baseline compliance level gave them a therapeutic dose – they of course remained in the therapeutic dose range but would not necessarily experience improved health outcomes.

It is important from a funder perspective that a change in compliance produces a clinically meaningful improvement in outcomes for at least some consumers. Ideally evidence for such claims would come from studies that are designed to measure compliance that also include measures of health outcomes. In the absence of such evidence, modelling of a relationship between compliance and an intermediate outcome, where good evidence exists to show that the intermediate outcome predicts longer-term health outcomes, may be useful. For example, if changes in compliance to combination products can be linked to greater reductions in established cardiovascular disease risk factors such as blood pressure and serum cholesterol level, existing evidence could be used to model the potential long-term benefits of improved

compliance. This would enable the PBAC to evaluate combination medicines using the same principles as those applied to other therapies.

However, the validity of modelling changes in compliance, measured over relatively short time periods to outcomes that occur over a lifetime is debated. As discussed in Part B, individuals on long-term therapies for chronic conditions may stop and restart taking their medicines, and modelling may not always accurately reflect this pattern of medicine use. However, where data are inadequate, modelling offers the only method for obtaining adequate evidence for funders to use in decisions on reimbursements.

C5 Financial Consequences: The Funder or Government Perspective

This Part should be read in conjunction with Point 6 in Table 3.

Key Point

- *Modelling the expected utilisation and costs of both comparator and combination items will be useful to Government to predict the possible impact on PBS budgets should a combination item be granted exemption from future mandatory price reductions.*

Given that many combination products are likely to replace widely-prescribed therapies for common indications such as cardiovascular disease, there can be substantial potential financial implications from exempting combination items that are demonstrated to improve compliance from future price reductions. An estimate of the likely cost of exempting a combination medicine from future price reductions, compared with the cost of the individual component medicines (that are not exempt from statutory price reductions), is therefore likely to be helpful. This process would involve projecting growth from current utilisation across both regimens (fixed combination and single component medicines) over four to five years. The different item prices could then be applied to each regimen to calculate the overall cost difference.

Glossary of terms

Acceptance - The consumer's informed decision to undertake behaviours that are expected to lead to improved health outcomes. In this report medicine taking is assumed to be part of the agreed regimen. (WHO, 2003)

Adherence - The extent to which the consumer conforms to the agreed behaviours, with respect to timing, dosage and frequency of medication taking. (Cramer, 2007a)

Alternative Therapies - are the therapies that are most likely to be used instead of or in place of the medicine of interest. Alternative therapies may be any treatment or medicine in any form: single component; modified release; or combination medicine.

Association - A statistical dependence between two or more events, characteristics or variables. An association exists when the value of one predicts the value of the other(s) more often than could occur by chance, but this does not necessarily imply a causal relationship.

Bias - the deviation of results or inferences from the truth, or processes leading to such deviation (whether intended or not); an alternative explanation for an apparent treatment effect.

Categorical data - Data in which the variables can only have discrete values.

Cohort study - An observational study in which two or more sub-sets of defined populations are identified by the presence of a common factor or factors (eg non-randomly assigned to therapy involving the proposed drug or to therapy involving the main comparator(s)) and then followed in time to investigate the influence of the factors on the probability of occurrence of an outcome or outcomes.

Concordance - refers to the nature of the interaction and establishment of a therapeutic alliance between clinician and patient, rather than the patient's medication taking behaviour. It is based on the notion that consultations between clinicians and patients are a negotiation between equals (Bell et al 2007)

Confounding - The distortion of a measure of the effect of an exposure (eg to therapy involving the proposed drug) on the risk of an outcome under investigation brought about by the association of the exposure with other factor(s) that can influence the outcome.

Class - A group of drugs with the same or similar pharmaceutical mechanism of action. These drugs may or may not have the same basic chemical structure. However, there may be differences between drugs within a class, for example, in side-effect profile.

Compliance - In this report, the term 'compliance' has been used in the broadest sense to encompass all aspects of consumers' acceptance, adherence and persistence with a prescribed medicine regimen.

Concomitantly – refers to taking more than one medicine at the same time, or concurrently.

Combination Items – are those fixed combination products that are listed as separate items (according to strength) on the PBS and belong to the CIL.

Continuous data - Data with a potentially infinite number of possible values along a continuum (eg age, height).

Co-payment - A payment made by the user at the time of service as part of the total payment for that service and any associated product.

Correlation - see association

Cost-effective - A proposed drug is considered cost-effective by PBAC if the Committee considers that, for a specified main indication, the incremental benefits of therapy involving the proposed drug over therapy involving its main comparator(s) justify its incremental costs and harms.

Dichotomous data - Data that are classified into either one of two mutually exclusive values, for example, 'yes' and 'no' or 'cured' and 'not cured.'

Economic evaluation - A comparative analysis of the costs and outcomes of therapy involving the proposed drug and therapy involving its main comparator(s). This is an umbrella term covering CBA, CEA, CMA and CUA. The analysis involves identification, measurement and valuation of the differences in costs and outcomes caused by substituting therapy involving the proposed drug for therapy involving its main comparator(s).

Effectiveness - The extent to which a therapy produces a benefit in a defined population in uncontrolled or routine circumstances.

Estimate - The value of a quantity which is known, believed or suspected of incorporating some amount of error.

Fixed Combination Medicines (products) - applies both to a combination of two or more active drugs in a single dosage form and to individual dosage forms in composite packaging.

Funder - In this report the funder refers to the entity that is responsible for subsidising the majority of the costs associated with the therapeutic use of a medicine. In Australia, for PBS listed medicines the funder is the Department of Health and Ageing.

Health outcome - A change (or lack of change) in health status caused by a therapy or factor when compared with a previously documented health status using disease-specific measures, general quality of life measures or utility measures.

Incremental cost-effectiveness ratio (ICER) - A comparison of two alternative therapies calculated by dividing the incremental costs from substituting the proposed drug for its main comparator by the incremental health outcomes from this substitution.

Index script or prescription - The first record a prescription in the database according to the rules outlined in the study.

Internal validity - A trial has internal validity if, apart from possible sampling error, the measured difference in outcomes can be attributed only to the different therapies assigned.

Kaplan-Meier curve - A graphical display of the results of a nonparametric method of compiling time to event tables. The method combines calculated probabilities of the event occurring with estimates to allow for censored observations, which are assumed to occur randomly. The resulting intervals are defined as ending each time an event (death, withdrawal) occurs and are therefore unequal.

Main comparator - (as refered to in Subsection A.4 Guidelines for submissions to PBAC) The therapy that prescribers would most replace with the proposed drug in practice if the PBS subsidises the proposed drug as requested.

Medication Possession Ratio (MPR) - A commonly-used calculation of medication adherence (Peterson, 2007; Andrade, 2006; Vink, 2008). It is calculated by summing the number of days supplied for all but the last prescription, divided by the number of days between supply of the first and the last prescription. When the MPR is calculated over different or flexible periods of supply it is called MPR flexible (MPRF) This measure is expressed as a percentage and disregards persistence. MPR can also be calculated for fixed time period such as a year (MPRY). This method has regard for both adherence and persistence if all participant begin their fixed period of observation at the time they initiate therapy.

Net cost - the monetary value of any increase in resource provision minus any cost off-sets, for example, those resulting from an improvement in outcome.

Observational study - A non-randomised study that observes the characteristics and outcomes over time of participants who do and do not take a particular therapy. This is an umbrella term for cohort and case-control studies.

Permissible or Allowable Gap – the time period allowed (as defined in a study protocol) to refill a consecutive prescription and be considered persistent.

Prescription refill - administrative record of a prescription that has been filled.

Proportion of Days Covered (PDC) - a common measure of persistence that is similar to the MPRY in that a specified time period (expressed in days) constitutes the denominator. However, the numerator is not the sum of the days of supply according to the prescriptions filled in the specified time period, but is adjusted for overlapping days or gaps in possession. The PDC is expressed as a percentage and is always a value between 0 and 1. (Peterson, 2007)

Quality use of medicines - The quality use of medicines involves the judicious selection of management options; the appropriate choice of medicines, where a medicine is considered necessary; and the safe and effective use of medicines.

Quality-adjusted life-year (QUALY) - number of years of life weighted by a utility value of the relative quality of life experienced.

Randomisation - The process by which participants are allocated to one of two or more therapy groups by chance and thus minimise selection bias. Other than chance variation, the resulting groups are also likely to be similar to one another at the start of the trial. Randomisation involves application of a predetermined plan to ensure that chance alone determines allocation to therapy groups.

Refill Gap - the days or period of time and individual takes to fill a second or consecutive prescription.

Refill Sequence - the sequence or pattern of prescriptions filled over a period of time.

Selection bias - Error due to systematic differences in characteristics between those who are selected for study and those who are not.

Statistically significant - The probability that the association between the factor and the outcome is due to chance is less than a specified level (by convention, $P < 0.05$).

Persistence - The duration of time from initiation to discontinuation of therapy. (Cramer, 2007a)

Variable - Any attribute, phenomenon or event that can have different values.

References

Andrade SE, Kahler KH, Frech F, Arnold K. 2006. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and Drug Safety* vol 15 pp 565-574.

Avorn J, Monette J, Lacour A, Bohn R, Monane M, Mogun H et al. 1998. Persistence of Use of Lipid-Lowering Medications: a cross-national study. *Journal of the American Medical Association* vol 279(18) pp 1458-62.

Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. 2007. Fixed dose combinations improve medication compliance: A meta-analysis, *American Journal of Medicine* vol 120 pp 713-719.

Baser O, 2009, Too Much Ado about instrumental variable approach: Is the cure worse than the Disease. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, May 19 (Epub ahead of print).

Berger M, Mamdani M, Atkins D and Johnson ML. 2009 Good research practices for defining, reporting and interpreting non-randomised studies of treatment effects using secondary database: report of the ISPOR Retrospective Database Analysis Task Force – Part I (in press).

Betancourt J.R. Carrillo JE and Green AR. 1999 Hypertension in multicultural and minority populations: linking communication to compliance, *Current Hypertension Reports*, vol 1 pp 482–488.

Bissonnette J. 2008 Adherence: a concept analysis. *Journal of Advanced Nursing*, vol 63(6) pp 634-643.

Bonaccorso S & Sturchio J. 2003. Perspectives from the pharmaceutical industry. *British Medical Journal*, vol 327 pp 863-4.

Britten N. 2003. Commentary: Does a prescribed treatment match a patient's priorities? *British Medical Journal*, vol 327 p840

Caetano PA, Lam J, Morgan SG. 2006. Towards a standard definition and measurement of persistence with drug therapy: examples from research in statins and antihypertensive utilisation. *Clinical Therapeutics*, vol 28(9) pp 1411-1424.

Chewning B. 2006. Commentary: The health adherer and the placebo effect. *British Medical Journal*, vol 333 pp18-19.

Choudhry NK, Shrank WH, Levin RL, Lee JL, Jan SA, Brookhart MA, Solomon DH, 2009, Measuring Concurrent Adherence to Multiple Related Medications. *The American Journal Of Mananged Care*. Vol 15, No 7 pp 457-463.

Cook CL, Wade WE, Martin BC, Perri M, 2005, Concordance among three self reported measures of medication adherence and pharmacy refill records. Journal of the American Pharmacists Association, Vol 45, No 2, pp 151 - 159.

Commonwealth of Australia. 2008. *Privacy Guidelines for the Medicare Benefits and Pharmaceutical Benefits Programs* (issued March 2008 - effective from 1 July 2008) available at www.privacy.gov.au/materials/types/guidelines/view/6576.

Cox E. Martin B, van Staa T, Garbe E, Siebert U, Johnson ML, 2009, Good research practices for designing non-randomised studiesof treatment effects using secondary databases: report of the ISPOR Retrospective Database Analysis Task Force – Part II. Available at http://www.ispor.org/TaskForces/documents/ISPORDRAFT-designingNRSTXeffct2ndDB.pdf (accessed 28/09/2009)

Cramer JA. 1995. Partial Medication Compliance: The Enigma in Poor Medical Outcomes. *The American Journal of Managed Care*, vol 1(2) 167-173.

Cramer JA, Roy A, Burrell A, Fairchild C, Fuldeore M, Ollendorf DA, Wong PK, (International Society for Pharmacoeconomics and Outcomes Research Working Group). 2007a. Medication compliance and persistence: Terminology and definitions, *Value in Health,* Vol 11 (1) p. 44-47.

Cramer JA, Silverman SL, Gold DT. 2007b. Methodological considerations in using claims databases to evaluate persistence to bisphosphonates. *Current Medical Research Opinion,* Oct;Vol 23(10) p 2369-77.

Department of Health and Ageing (DoHA). *Pharmacy and Government Arrangements – Fourth Community Pharmacy Agreement 2005* available at www.health.gov.au accessed 12 January 2010.

Department of Health and Ageing (DoHA). 2008. Guidelines for preparing submissions to the PBAC. Available at http://www.health.gov.au/internet/main/publishing.nsf/content/pbacguidelines-index accessed 12 January 2010.

Dezil CM, 2000, A retrospective study of persistence with single-pill combination therapy vs. concurrent two-pill therapy in patients with hypertension. *Managed Care*, vol 9(9) pp S2-S6.

Dickson m, Plauschinat CA, 2008, Compliance with Antihypertensive Therapy in the Elderly A Comparison of Fixed-Dose Combination Amlodipine/Benazepril versus Component-Based Free-Combination Therapy. *American Journal of Cardiovascular Drugs,*Vol 8, No 1, pp 45-50.

DiMatteo MR, Giordani PJ, Lepper HS & Croghan TW. 2002. Patient Adherence and Medical Treatment Outcomes: a meta-analysis. *Medical Care*, vol 40(9) pp 794-811.

DiMatteo MR. 2004. Variations in Patients' Adherence to Medical Recommendations: a quanitative review of 50 years of research. *Medical Care* vol 42(3) pp 200-209.

Gunderson, J.G. 1990. The role of the therapeutic alliance in the treatment of schizophrenia: relationship to course and outcome. *Archives of General Psychiatry*, vol 47 pp 228-236.

Gadzhanova S, Roughead E, Mackson J, 2009, Anticholinesterase duration in the Australian veteran population. *Australian and New Zealand Journal of Psychiatry* (in press).

Green JL, Hawley JN, Rask KJ. 2007. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? American Journal of Geriatric Pharmacotherapy. 5 (1) March: pp31-39.

Grol R & Buchan H. 2006. Clinical guidelines: what can we do to increase their use? Editorial, *Medical Journal of Australia*, vol 185(6) p 301.

Grossberg R and Gross R. 2007. Use of Pharmacy Refill Data as a Measure of Antiretroviral Adherence. *Current HIV/AIDS Reports*, vol 4 pp 187-191.

Grymonpre R, Cheang M, Fraser m, Metge C, Sitaar DS. 2006. Validityof prescription claims database to estimate medication adherence in older persons. *Medical Care*, Vol 44, No 5, pp: 471-477.

Gwadry-Sridhar FH, Manias E, Zhang Y, Roy A, Yu-Isenberg K, Hughes DA & Nichol MB. 2009. A checklist for medication compliance and persistence studies using prospective study designs. *Clinical Therapeutics*, vol 31(2) pp 421-435.

Hansen RA, Kim MM, Song L, Tu W, Wu J & Murray MD 2009. Comparison of methods to assess medication adherence and classify nonadherence. *Annals of Pharmacotherapy*, vol 43 pp413-422.

Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. 2005. Interventions to enhance medication adherence. *Cochrane Database Systematic Review*. Available at www.mrw.interscience.wiley.com/cochrane accessed on 11 January 2009.

Heath I. 2003. A Wolf in Sheep's Clothing: a critical look at the ethics of drug taking. *British Medical Journal*, vol 327 pp 856-858.

Hotopf , M. 2002. The Pragmatic Randomised Controlled Trial. *Advances in Psychiatric Treatment*, vol 8, p. 326-333.

Hudson M, Rahme E, Richard H, Pilote L. 2007. Comparison of Measures of medication persistencey using a prescription drug. A*merican Heart Journal*, vol Jan; 153(1) pp 59-65.

Hughs D, Cowell W, Koncz T, Cramer J et. al. (International Society for Pharmacoeconomics Research - Economics of Medication Compliance Working Group) 2007. Methods for integrating medication compliance and persistence in pharmacoeconomic evaluations. *Value Health*, vol Nov-Dec 10(6) pp 498-509.

Hynd A, Roughead E, Preen D, Glover J, Bulsara M and Semmens J. 2008. The impact of Co-payment Increases on Dispensings of Government-subsidised Medicines in Australia. *Pharmacoeipemiology and Drug Safety*, vol 17 pp 1091-1099.

Jackson S, Naunton M, Peterson G, 2006, Medication Adherence. Pharmaceutical Society of Australia, ACT, ISBN: 0-908185-84-7.

Johnson ML, Crown W, Martin B, Dormuth C and Siebert U. 2009. Good research practices for the analysis of non-randomised studies of treatment effects using secondary databases. Report of the ISPOR Retrospective Database Analysis Task Force – Part III

Jones G. 2003. Prescribing and taking medicines. Editorial, *British Medical Journal*, vol 327 pp 819.

Kalisch LM, Roughead EE and Gilbert AL. 2007. Pharmaceutical brand substitution in Australia – are there multiple switches per prescription? *Australian and New Zealand Journal of Public Health*, vol 31(4) pp 348-352

Karve S, Cleves MA, Helm M, Hudson TJ, West DS and Martin BC. 2008. An empirical basis for standardising adherence measures derived from administrative data among diabetic patients. *Medical Care*, Vol 46, No 11, pp 1125-1133.

Kothawala P, Badamgarav E, Ryu S, Miller RM and Halbert RJ. 2007. Systematic Review and meta-analysis of real world adherence to drug therapy for osteoporosis. *Mayo Clinic Proceedings*, vol 82(12) pp 1493-1501.

Krueger KP, Berger BA and Felkey B. 2005. Medication adherence and persistence: a comprehensive review. *Advances in Therapy*, vol 22(4) pp 313 – 340.

Kwon A, Bungay KM, Rogers WH, Wilson IB, Zhou Q, Adler DA, 2003, Antidepressant use: Concordance between self report and claims records. *Medical Care*, Vol 41, No 3, pp: 368-374.

Lee PP, Walt JG, Chiang TH, Guckian A and Keener J. 2007. Gap Analysis approach to assess patient persistence with glaucoma medication. *American Journal of Opthalmology*, vol 144 (4) pp 520-4.

Legorretta A, Yu A, Chernicoff H, Gilmore A, Jordan J, Rosenzweig JC, 2009, Adherence to combined Lamivudine Zidovudine versus individual components: A community –based retrospective Medicaid claims analysis. Aides Care, Vol 17, No 8, pp 938-948.

Manias, E, Claydon-Platt, K., Mccoll, G.J., Bucknall, T.K. and Brand, C.A. 2007. Managing complex medication regimens: perspectives of consumers with osteoarthritis and health professionals. *Annals of Pharmacotherapy*, vol 41(5) pp 764-771.

Marder SR; Mebane A, Chien C-R, Winslade WJ, Swann E and Van Putten TA. 1983. Comparison of patients who refuse and consent to neuroleptic treatment. *American Journal of Psychiatry*, vol 140(4) pp 470-472.

McDermott MM, Schmitt B, Wallner E. 1997. Impact of medication nonadherence on coronary heart disease outcomes. A critical review. *Arch Intern Med*, 157(17):1921-9, 1997 Sep 22.

Medicare Australia. 2009a. *Home Medicines Reviews* available at www.medicareaustralia.gov.au/provider/pbs/fourth-agreement accessed on 11 January 2010.

Medicare Australia. 2009b. *PBS Safetynet* available at www.hic.gov.au/public/services/msn/pbs accessed on 12 January 2010

Melikian C, White TJ, Vanderplas A, Dezii C and Chang E. 2002. Adherance to oral antidiabetic therapy in a managed care organisation: a comparison of monotherpy, combination therapy and fixed dose combination therapy. *Clinical Therapeutics*, vol 24 (3) pp 460-467.

Morris LS and Schulz RM. 1993. Medication compliance: the patient's perspective. *Clinical Therapeutics*, vol 15 pp 593-606.

Motheral BR, Fairman KA, 1997, The Use of Claims Databases for Outcomes Research: Rationale , Challenges and Strategies. Clinical Therapeutics, Vol 19, No 2, pp 346-364.

Moulds RF. 2001. Combination Products – love them or loathe them? Australian Prescriber, vol 24, p. 127-9.

National Institute for Health and Clinical Excellence (NICE). 2009. *Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence*. Clinical Guideline 76

National Prescribing Service (NPS). 2007. *Adherence, Compliance, Concordance and Persistence* (unpublished)

Ortiz M, Calcino G. 2009a. Time to restart after stopping antihypertensive treatment, *unpublished paper*.

Ortiz M, Calcino G. 2009b. Differences in treatment persistence when dihydropyridines are added to other antihypertensives, *unpublished paper*.

Ortiz M, Calcino G. 2009c. Differences in treatment persistence over time between dihydropyridine antihypertensives, *unpublished paper*.

Ortiz M, Calcino G. 2009d. Inferred mortality differences between dihydropyridine antihypertensives, *unpublished paper*.

Osterberg L. 2005. Adherence to Medication. *The New England Journal of Medicine*, vol 353(5) pp 487-197.

Patel BV, Remigio-Baker R, Thiebaud P, Preblick R and Plauschinat C. 2008. Improved persistence and adherence to diuretic fixed-dose combination therapy compared to diuretic monotherapy. *BMC Family Practice*, vol 9: pp 61.

Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C Wagener MM, Singh N. (2000) Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Annals of Internal Medicine. 133(1), 21-30.

Perreault S, Dragomir A, White m, Lalonde L, Blais L, Be´ rard A, 2009, Frank AF & Better adherence to antihypertensive agents and risk reduction of chronic heart failure. *Journal of Internal Medicine*, doi: 10.1111/j.1365-2796.2009.02084.x

Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F and Nichol M. 2007. A checklist for medication compliance and persistence studies using retrospective databases. *Value in Health*, vol 10(1) pp 3-12.

Pound P, Britten N, Morgan M, Yardley L, Pope C, Daker-White G, Campbell R, 2005, Resisting medicines: a synthesis of qualitative studies of medicine taking. *Social Science and Medicine*, Vol 61, pp 133-155.

Quality Medication Care Group. 2004. Effectiveness and cost effectiveness of dose administration aids. Available at www.guild.org.au/research/funded_projects.asp accessed 17 July 2009.

Roughead EE, Ramsay E, Pratt N and Gilbert AL. 2008. NSAID use in individuals at risk of renal adverse events: an observational study to investigate trends in Australian Veterans. *Drug Safety*, vol 31(11) pp 997-1003.

Roughead EE, Barratt JD, Ramsay JD, Pratt N, Ryan P, Peck R, Killer G and Gilbert AL, 2009a, The effectiveness of collaborative medicine reviews in delaying time to next hospitalisation for patients with heart failure in the practice setting: results of a cohort study. *Circulation: Heart Failure*, vol 2(5) pp424-428.

Roughead EE, Vitry AI Preiss AK, Barratt JD, Gilbert AL, Ryan P, 2009b, Assessing overall duration of cardiovascular medicines in veterans with established cardiovascular disease. *European Journal Cardiovascular Prevention and Rehabilitation*, 2009 Jul 6. (e-pub ahead of print).

Roughead EE, Ramsay E, Preiss K, Barratt J, Ryan P, 2009c, Medication adherence, first episode duration, overall duration and time without therapy: the example of bisphosphonates. *Pharmacoepidemiology and Drug Safety*, vol 18(1) pp 69-75.

Royal Pharmaceutical Society of Great Britain. 1997. *From Compliance to Concordance: Achieving Shared Goals in Medicine Taking.* London: Royal Pharmaceutical Society of Great Britain.

Segal JZ. 2007. “Compliance” to “Concordance”: A Critical View. *Journal of Medical Humanities*, vol 28 pp 81-96.

Shalansky SJ and Levy AR. 2002. Effect of number of medications on cardiovascular therapy adherence *Annals of Pharmacotherapy*, vol 36(10) pp 1532-9.

Sikka R, Xia F, Aubert RE. 2005. Estimating medication persistency using administrative claims data *American Journal of Managed Care*, vol 11 pp 449-457.

Simons LA, Ortiz M, Calcino G. 2008. Persistence with antihypertensive medication: Australia wide experience 2004-2006, Medical Journal of Australia, Vol 188, p. 224-7.

Simpson SH, Eurich DT, Sumit RM, Radjeedp SP, Ross TT, Varney J and Johnson J. 2006. A meta-analysis of the association between adherence to drug therapy and mortality. *British Medical Journal*, vol 333 pp15-18.

Urquhart J. 2001. Some Economic Consequences of Noncompliance. *Current Hypertension Reports*, vol 3 pp 473-80.

Van Bruggen R, Gorter K, Stolk R, Zuithoff P, Klungel OH, Rutten GE. 2009. Refill adherence and polypharmacy among patients with type 2 diabetes in general practice, *Pharmacoepidemiology and Drug Safety*, Accessed Online DOI: 10.1002/pds.1810

Vink NM, Klungel OH, Stolk RP and Denig P. 2009. Comparison of various measures for assessing medication refill adherence using prescription data. *Pharmacoepidemiology and Drug Safety*, vol 18(2) pp 93-174.

Wahl C, Gregoire JP, Teo K, Beaulieu M, Labelle S, Leduc B, Cochrane B, Lapointel L and Montague T. 2005. Concordance, compliance and adherence in health care: closing gaps and improving outcomes. *Healthcare Quarterly*, vol 8(1) pp 65-70.

White H.D. 2005. Adherence and outcomes: it’s more than taking the pills. *The Lancet*, vol 366(9502) pp 1989-1991.

World Health Organization. 2003. *Adherence to long-term therapies: evidence for action.* Geneva: WHO.

Appendix 1

1.Terms of Reference and Procedures of the Compliance Working Group

The Compliance Working Group is a working group of the Drug Utilisation Sub Committee (DUSC). DUSC is established as a sub-committee of the Pharmaceutical Benefits Advisory Committee (PBAC) under Section 101A of the National Health Act (1953).

1.1 Terms of Reference

Define terminology related to the investigation of compliance to medicinal therapy.

Ascertain relevant methods of comparing compliance across medicinal therapies by searching and appraising the relevant literature.

Explore and identify the limitations of these current study designs and analytical techniques used in the assessment of compliance to medication therapy, in particular combination items versus their components given concomitantly.

Examine the implications of relying on Australian versus non-Australian sources of evidence and using existing administrative databases rather than other approaches such as prospectively collecting data.

Prepare a report or discussion paper to inform and advise DUSC and PBAC on these matters within twelve months.

1.2 Reporting Structure

The Compliance Working Group reports to DUSC, and through DUSC to PBAC.

2. Composition and Membership of the Compliance Working Group

The Compliance Working Group has a membership of up to twelve people excluding the Chair person, PBAC Chair and Secretariat for the working group.

2.1 Composition

The Compliance Working Group is to be chaired by the DUSC chair, with the PBAC Chair to attend in an ex officio capacity. The proposed membership structure is:

Two (2) DUSC members

Two (2) PBAC members

Two (2) independent experts in pharmacoepidemiology and compliance

Three (3) nominees from Medicines Australia

One (1) nominee from Generic Medicines Industry Association

One (1) nominee from the National Prescribing Service (Evaluation Team)

One (1) nominee from Medicare Australia (statistical and compliance area)

One (1) consumer representative

2.2 Appointment procedures for Medication Compliance Working Group

DUSC will appoint members considering nominations from Medicines Australia, National Prescribing Service and Medicare Australia. DUSC will nominate other proposed members.

2.3 Period of membership

Individual members are appointed to the Working Group for a period twelve months.

2.4 Resignation

A member of the Working Group may resign in writing (to the Chair of DUSC). If so, the relevant nominating body will nominate a replacement for consideration of DUSC at its next meeting.

2.5 Remuneration

Voting members who are salaried staff of nominating organisations or other Commonwealth, State or Local Government agencies and who receive a salary from that organisation to attend Working Group meetings, do not receive remuneration for their attendance.

Standard fees as for attendance at DUSC may be made available for the independent expert members.

2.6 Attendance of members at Working Group Meetings

A member, including the Chair, is deemed to be present at a Working Group meeting if s/he attends in person or participates by telephone or closed circuit television.

It is proposed that the first meeting be face to face and subsequently most meetings will be via teleconference. There may be a need for a final face to face meeting.

2.7 Secretariat

Secretariat support for the Compliance Working Group is provided by the DUSC Secretary or a nominated staff member located in the Pharmaceutical Evaluation Section (PES) of the Pharmaceutical Benefits Branch (PBB).

2.8 Attendance of advisers at DUSC Reference Group meetings.

The Working Group may invite advisers to attend meetings as required, including officers of Department of Health and Ageing.

3. Compliance Working Group Membership

Chair

Professor Wayne Hall

Ex Officio PBAC Chair

Emeritus Professor Lloyd Sansom

Independent Experts (2)

1) Dr Philip Clarke

Senior Research Fellow, School of Public Health, The University of Sydney.

2) Professor Elizabeth Manias

Professor, Associate Head of Research Training Equity and Staff Development Coordinator School of Nursing Faculty of Medicine, Dentistry and Health Sciences The University of Melbourne, Victoria, Australia

Member of the ISPOR Medication Compliance and Persistence Special Interest Group – Determinants of Compliance and Persistence working group.

DUSC Members (2)

1) Assoc Prof Elizabeth Roughead

2) Dr Helen Toyne

PBAC Members (2)

1) Professor Michael Frommer

2) Dr Steve Hambleton (resigned May 09)

GMiA (1)

Ms Kate Lynch

Medicare Australia (1)

Mr Peter Thomson, Manager Research Information

National Prescribing Service (1)

Dr Jonathan Dartnell, Executive Manager, Innovation and Learning

Medicines Australia (3)

1) Dr Michael Ortiz, Manager, Pricing and Reimbursement

Abbott Products.

2) Mr Mike Smith, Manager, Health Economics & Pricing,

AstraZeneca,

3) Dr. Michael Adena

Datalytics

Consumer Representative

Mrs Janet McDonald

Department of Health and Ageing (Working Group Support)

Louise Bartlett

Maxine Robinson

Andrew Mitchell

Appendix 2

Combination items listed on the PBS as at 1 January 2010

ABACAVIR with LAMIVUDINE
ABACAVIR with LAMIVUDINE and ZIDOVUDINE
AMLODIPINE with ATORVASTATIN
AMLODIPINE with VALSARTAN
ATOVAQUONE WITH PROGUANIL
BIMATOPROST WITH TIMOLOL
BRIMONIDINE with TIMOLOL
BUDESONIDE with EFORMOTEROL
BUPRENORPHINE with NALOXONE
CALCIPOTRIOL with BETAMETHASONE
CANDESARTAN with HYDROCHLOROTHIAZIDE
CLOPIDOGREL WITH ASPIRIN
DIPYRIDAMOLE with ASPIRIN
DORZOLAMIDE with TIMOLOL
EPROSARTAN with HYDROCHLOROTHIAZIDE
ESOMEPRAZOLE and CLARITHROMYCIN and AMOXYCILLIN
ETIDRONIC ACID and CALCIUM
EZETIMIBE with SIMVASTATIN
FERROUS FUMARATE with FOLIC ACID
FLUTICASONE with SALMETEROL
GOSERELIN and BICALUTAMIDE
HYDROCHLOROTHIAZIDE with TRIAMTERENE
INSULIN ASPART-INSULIN ASPART PROTAMINE SUSPENSION
INSULIN LISPRO-INSULIN LISPRO PROTAMINE SUSPENSION
INSULIN NEUTRAL-INSULIN ISOPHANE
IRBESARTAN with HYDROCHLOROTHIAZIDE
LAMIVUDINE with ZIDOVUDINE
LATANOPROST with TIMOLOL
LEVODOPA with CARBIDOPA and ENTACAPONE
LOPINAVIR with RITONAVIR
METFORMIN with GLIBENCLAMIDE
NEOMYCIN with BACITRACIN
NORETHISTERONE with MESTRANOL
OESTRADIOL and OESTRADIOL with DYDROGESTERONE
OESTRADIOL and OESTRADIOL with NORETHISTERONE
OESTRADIOL with NORETHISTERONE
OESTROGENS-CONJUGATED with MEDROXYPROGESTERONE
OLMESARTAN with HYDROCHLOROTHIAZIDE
OMEPRAZOLE and CLARITHROMYCIN and AMOXYCILLIN
PREDNISOLONE with PHENYLEPHRINE
QUINAPRIL with HYDROCHLOROTHIAZIDE
RAMIPRIL with FELODIPINE
RIBAVIRIN and PEGINTERFERON ALFA-2a
RIBAVIRIN and PEGINTERFERON ALFA-2b
RISEDRONIC ACID and CALCIUM
RISEDRONIC ACID and CALCIUM with COLECALCIFEROL
ROSIGLITAZONE with METFORMIN
SITAGLIPTIN WITH METFORMIN

SODIUM CHLORIDE with GLUCOSE
TELMISARTAN with HYDROCHLOROTHIAZIDE
TENOFOVIR with EMTRICITABINE
TRANDOLAPRIL with VERAPAMIL
TRAVOPROST with TIMOLOL
VALSARTAN with HYDROCHLOROTHIAZIDE

Appendix 3

Sources of data for pharmaceutical research

This document is regularly updated. For the most current version please contact Louise Bartlett or Chris Raymond in DUSC Secretariat, louise.bartlett@health.gov.au