CENTRE FOR THE
HEALTH ECONOMY

MACQUARIE
University

# An economic evaluation framework to inform the scheduling of medicines

PREPARED FOR

AUSTRALIAN SELF MEDICATION INDUSTRY LTD

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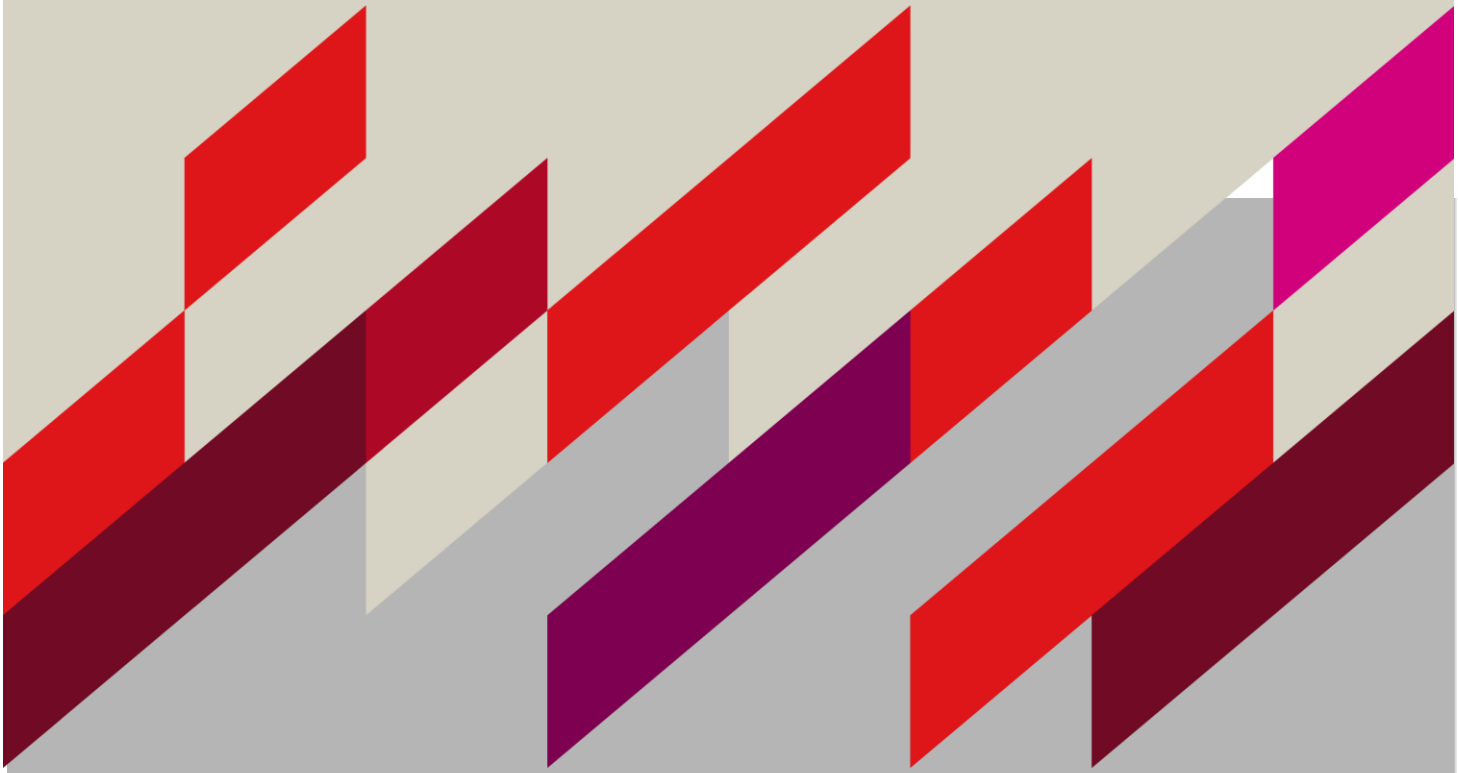

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# About MUCHE

Macquarie University is recognised as one of Australia's leading research universities, with an enviable reputation for excellence. While still relatively young, success of the past 50 years has positioned our distinctive approach to deliver ground-breaking research with world-changing impact.

Recently, we have invested heavily in infrastructure, with over $1 billion spent on facilities and buildings. We have also significantly expanded our teaching and research capacity in health, for example, with the development of a new Faculty of Medicine and Health Sciences, and relocation of the Australian Institute of Health Innovation from the University of NSW.

The University's objectives are to accelerate world-leading research; to prepare world-ready higher degree research candidates; to actively engage externally as a world-recognised research collaborator and partner of choice. We believe collaborating with industries, governments, communities, professions and academic colleagues around the world is paramount to our success.

Macquarie University's Centre for the Health Economy (MUCHE) was recently established as a strategic initiative to undertake innovative research on health, ageing and human services. Our vision is to create a world where decision makers are empowered with applied, trusted and influential research into health and human services policy and systems. Our mission is to deliver leading innovative research by operating professionally, collaboratively and sustainably.

To this end, we undertake research for government, business, and not-for-profit organisations, which is used to inform public debate, assist decision-making, and help formulate strategy and policy.

We are interested in investigating the Health Economy at the macro level, with particular focus on the interdependencies of these systems with each other, and the broader economy. This includes investigating factors beyond the health and human services sectors that impact the health and wellbeing of populations.

Our point of difference lies in our approach to research. While MUCHE primarily consists of specialist health economists, we recognise that researching the Health Economy requires many skill sets and experience. Solving problems within health and human services now requires teams with multi-disciplinary skills working closely together.

We therefore work collaboratively with our partners, and across the University, including the Faculty of Business and Economics, Faculty of Human Sciences, and the Faculty of Medicine and Health Sciences. We also work with Macquarie University's world renowned research hubs, such as partners within the Australian Hearing Hub and the Australian Institute of Health Innovation.

We take pride in combining our professional approach to partner engagement, with our academic approach to methodology, to deliver innovative translational research.

Dr Henry Cutler
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# Contents

# Glossary

| Term | Meaning |
|---|---|
| 95%CI | 95% confidence interval |
| A$ | Australian dollar |
| ABS | Australian Bureau of Statistics |
| Accidental ingestion | Non-intentional use of a medicine, usually by a child |
| ACMS | Advisory Committee of Medicines Scheduling |
| ADRAC | Adverse Drug Reactions Advisory Committee |
| AIDS | Acquired immunodeficiency syndrome |
| ALSWH | Australian Longitudinal Study on Women's Health |
| AMPP | American Migraine Prevalence and Prevention |
| AQOL | Assessment of Quality of Life |
| ATSI | Aboriginal and Torres Strait Islander |
| AUST L | Listed medicines on the ARTG |
| AUST R | Registered medicines on the ARTG |
| AIHW | Australian Institute of Health and Welfare |
| AR-DRG | Australian Refined Diagnosis Related Groups |
| ARTG | Australian Register of Therapeutic Goods |
| BEACH | Bettering the Evaluation and Care of Health |
| CEAC | Cost-effectiveness acceptability curve |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CI | Confidence interval |
| DPMQ | Dispensed price for maximum quantity |
| DVT | Deep vein thrombosis |
| ECG | Electrocardiogram |
| ED | Emergency department |
| EQ-5D-3L | Euroqol five-dimension three-level |
| EQ-5D-5L | Euroqol five-dimension five-level |
| FBC | Full blood count |
| FDA | United States Food and Drug Administration |
| g | Gram |
| GBP | Great British Pounds |
| GDP | Gross domestic product |
| GP | General practitioner |
| HD | High dose |
| HILDA | Household, Income and Labour Dynamics in Australia |
| HIT | Headache Impact Test |
| HIV | Human immunodeficiency virus |

| Term | Meaning |
|---|---|
| HPV | Human papillomavirus |
| HUI2 | Health Utilities Index Mark 2 |
| HUI3 | Health Utilities Index Mark 3 |
| IBMS | International Burden of Migraine Study |
| ICD | International Classification of Diseases |
| ICER | Incremental cost-effectiveness ratio |
| Intentional overdose | Use of more than the recommended dose for self-harm |
| Intentional misuse with therapeutic intent | Use of more than the recommended dose due to perceived inadequate efficacy or a belief that OTC medicines are less effective, or using the medicine for an extended period. |
| IUD | Intrauterine device |
| LARC | Long acting reversible contraception |
| LD | Low dose |
| LSD | Lysergic acid |
| ln | Natural logarithm |
| MAUI | Multi-attribute utility instrument |
| MBS | Medical Benefits Scheme |
| MCA | Multiple Criteria Analysis |
| MDMA | 3,4-methylenedioxy-amphetamine |
| MeSH | Medical Subject Headings |
| mg | Milligrams |
| MI | Myocardial infarction |
| ml | Millilitres |
| Mm Hg | Millimetres of mercury |
| N | Number of patients |
| NDPSC | National Drugs and Poisons Schedule Committee |
| NEC | Not elsewhere classified |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NPS | National Prescribing Service |
| NSAID | Non-steroidal anti-inflammatory drug |
| NSW | New South Wales |
| OCP | Oral contraceptive pill |
| ODT | Oral disintegrating tablet |
| OR | Odds ratio |
| OTC | Over-the-counter |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PBS | Pharmaceutical Benefits Scheme |
| PE | Pulmonary embolism |
| PICO | Population, Intervention, Comparator, Outcome |

| Term | Meaning |
|---|---|
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PROMIS GSF | Patient reported outcomes measurement information system global short form |
| PSA | Probabilistic sensitivity analysis |
| PVSA | Post-vasectomy semen analysis |
| QALY | Quality-adjusted life year |
| QWB | Quality of Well Being |
| RCT | Randomised controlled clinical trial |
| RPBS | Repatriation Pharmaceutical Benefits Scheme |
| Rx | Prescription |
| RR | Relative risk |
| SD | Standard dose |
| SE | Standard error |
| SEK | Swedish Kroner |
| SF-6D | Short-form six-dimension |
| Schedule 2 | Medicines listed under Schedule 2 of the SUSMP. These medicines may be available on the shelf at pharmacies. If required, advice from a pharmacist or pharmacy assistant should be available. |
| Schedule 3 | Medicines listed under Schedule 3 of the SUSMP. These medicines are available behind the pharmacy counter. A pharmacist must be consulted before dispensing. |
| Schedule 4 | Medicines listed under Schedule 4 of the SUSMP. These medicines are available only with a prescription. |
| Schedule 8 | Medicines listed under Schedule 8 of the SUSMP. These medicines are only available with a prescription but are at risk of abuse, misuse, or physical or psychological dependence. |
| SG | Standard gamble |
| SSRI | Selective serotonin reuptake inhibitors |
| SNRI | Serotonin–norepinephrine reuptake inhibitors |
| STI | Sexually transmitted infection |
| SUSMP | Standard for the Uniform Scheduling of Medicines and Poisons |
| TIA | Transient ischaemic attack |
| TGA | Therapeutic Goods Administration |
| TTC | Trying to conceive |
| TtM | The Australian Longitudinal Study on Male Health |
| TTO | Time trade-off |
| UK | United Kingdom |
| US | United States of America |
| VTE | Venous thromboembolism |

# Executive summary

***Use and access to over-the-counter medicines in Australia***

Australia spent $161.6 billion on healthcare in 2014–15, which accounted for 10.0% of gross domestic product (GDP).[1, 2] Expenditure on medicines represented around 12.3% ($19.8 billion) of all healthcare spending. While the majority of medicines used to treat Australians require a prescription, medicines used for self-medication represented 26% of the total expenditure on medicines in Australia in 2016.[3] Most Australians have self-medicated in the past year with over-the-counter (OTC) medicines and complementary medicines.[4]

In Australia, the *Poisons Standard* sets out the degree of control over the availability of medicines and poisons to the public.[5] Initially patients require a prescription to access most new medicines. Decision makers may later 'switch' or 'down-schedule' these medicines to being available OTC. Decision makers largely focus on patient risk when making decisions about whether to restrict a medicine to prescription only or allow it to be available OTC (also known as scheduling decisions).[6] Decision makers especially consider the risk of inaccurate or delayed diagnosis, the risk of inappropriate use, the incidence and severity of adverse events, and the need for advice from a medical practitioner or pharmacist.

However, there are also benefits to the patient and the healthcare system from allowing a medicine to be available OTC. It may improve patient health outcomes by reducing barriers to treatment. This may reduce the time to symptom relief, and improve treatment rates and adherence. Reducing barriers to treatment may also encourage patients to switch to more effective or safer treatments. Consequently, health-related quality of life may be improved, the onset of related diseases may be prevented, or disease progression may be delayed.

Allowing a medicine to be available OTC may reduce general practitioner (GP) attendances for common conditions. Furthermore, improved health outcomes may lead to less demand for healthcare, such as diagnostic tests and hospitalisations. These resources could be used to diagnose and treat other patients. This could reduce the pressure on Government budgets.

Whether the benefits of down-scheduling a medicine to being available OTC outweigh the risks largely depends on the medicine under consideration. Decision makers in Australia may already consider these benefits, although they may be given less importance as they are not included in the formal list of factors to be considered.[6] Research suggests that while Australia was previously active in down-scheduling medicines compared to the rest of the world, in recent years Australia has adopted a more conservative approach.[7]

An external review of medicines and medical devices regulation was conducted for the Australian Federal Minister for Health in 2015.[8] The review recommended that the framework used to determine scheduling decisions be reviewed and suggested that a formal risk-benefit framework may assist.

***Research objectives***

This report presents an economic evaluation framework to help inform scheduling decisions regarding whether a medicine should be available via prescription only (Schedule 4 in Australia) or Pharmacist Only (Schedule 3 in Australia). The economic evaluation framework is an extension of the Brass framework[9], and is based on various guidelines currently available regarding how to conduct a health economic evaluation, or part thereof[10-22], however with some adjustment to focus it towards informing scheduling decisions.

The application of the economic evaluation framework is demonstrated using two case studies: down-scheduling triptans and down-scheduling the oral contraceptive pill (OCP).

### *Strengths of the economic evaluation framework to inform the scheduling of medicines*

It is not possible to conduct randomised controlled trials (RCT) of scheduling decisions given that they are applied nation-wide. As a solution, the framework suggests a methodological approach typically used in economic evaluations, namely economic modelling, to synthesise data from a variety of sources. Economic modelling would enable decision makers to consider a broad range of benefits and risks, their likelihood of occurring, and the magnitude of their impact on health outcomes and resource use. It could also be used to predict the overall impact of a scheduling decision on health outcomes and resource use before it occurs.

The economic evaluation framework also recognises that re-scheduling a medicine can result in a wide range of health outcomes, including symptom severity and duration, incidence and progression of diseases, and adverse events. Health outcomes can be aggregated to a single measure – Quality Adjusted Life Years (QALYs), which incorporates life expectancy and quality of life, and the strength of community preferences across these domains.

In addition to considering the impact on health outcomes, the economic evaluation framework includes the impact on healthcare resource use and costs. Healthcare resources are both valuable and scarce. Their use generates an opportunity cost because they could be used to treat other patients and reduce waiting times.

The economic evaluation framework recognises that scheduling decisions may improve or reduce overall health outcomes, and increase or decrease costs associated with healthcare resource use. If re-scheduling a medicine reduces health outcomes, then it is questionable whether the schedule change should go ahead. Alternatively, if re-scheduling a medicine improves health outcomes and lowers costs, then there is strong support for the schedule change. But the appropriate scheduling decision is less clear if re-scheduling a medicine improves health outcomes and increases costs. In this case, decision makers can use the incremental cost-effectiveness ratio (ICER) to assess whether the schedule change is 'value for money'.

Finally, the economic evaluation framework recognises that scheduling decisions are often based on limited data, especially regarding patient behaviour, the risk of adverse events and possible benefits. It is important to avoid making an inappropriate scheduling decision, as this would result in poorer health outcomes and poorer use of healthcare resources. However, the presence of uncertainty in the evidence is not the same as uncertainty in the regulatory decision.

Sensitivity analysis can facilitate the assessment of whether uncertainty in the evidence results in uncertainty in the scheduling decision. It can enable decision makers to assess the importance of a certain parameter and whether re-scheduling should be delayed until further research is conducted. This avoids the risk of placing too much or too little importance on risks or benefits where the clinical impact or the frequency of events are unknown due to limited data. It can also enable decision makers to assess the impact of different regulatory scenarios on health outcomes and resource use, and whether only a sub-group of patients should access a medicine OTC. Probabilistic sensitivity analysis can estimate the probability that re-scheduling a medicine is cost-effective.

### *Demonstration of the framework*

The application of the economic evaluation framework is demonstrated using two Australian case studies. The purpose of these case studies is to illustrate the potential usefulness of an economic evaluation approach to scheduling decisions, by synthesising a wide variety of evidence, considering a broader range

of benefits and risks, ensuring consistency across submissions, and assessing uncertainty and whether further research is required.

Down-scheduling triptans

The first case study applies the economic evaluation framework to estimate the cost-effectiveness of down-scheduling triptans from prescription only (Schedule 4) to Pharmacist Only (Schedule 3) in Australia.

Migraine is a common, chronic, disabling headache disorder. While there is no cure for migraine, there are several pharmacological and non-pharmacological treatments available for the prevention of migraines and treatment of acute attacks. Given an attack occurs, acute treatments aim to reduce the pain severity and migraine duration, including triptans. Triptans are available via prescription in Australia, however they are available OTC in several developed countries. Down-scheduling triptans will help patients self-medicate when a migraine is in its early onset stage before symptoms have progressed.

A decision analytic model was used to synthesise data from a variety of sources. Behaviour before down-scheduling was estimated using medical practitioner survey data and Pharmaceutical Benefits Scheme (PBS) data, while behaviour after down-scheduling was estimated using patient survey data.

Health outcomes included the frequency and duration of migraines, pain free and relief at two hours following treatment, and the incidence of adverse events (fatigue, dizziness, nausea, chest discomfort, myocardial infarction, stroke, arrhythmia, angina, transient ischaemic attack (TIA), dyspepsia, serotonin syndrome, and death) and QALYs. The analysis also considered the risk of chronic headache, also known as medication overuse headache or rebound headache (defined as headache occurring ≥ 15 days per month). Some adverse events are more common with triptans, while others are more common with other treatments for migraines.

Costs included those related to GP consultations, medicines, pharmacist time, emergency department visits, hospitalisations, and adverse events.

It was predicted that down-scheduling triptans will reduce the duration of migraines, but increase the number of patients experiencing adverse events. However, overall it was predicted that down-scheduling triptans would result in 337 QALYs gained at a cost of $5.9 million over ten years. While down-scheduling was not predicted to be cost-saving, the ICER was estimated to be $17,412 per QALY gained. This is within the range generally considered to be ‘value for money’ or ‘cost-effective’ by decision makers in Australia.

Serotonin syndrome, a key concern of the TGA committee, had little impact on the results. Further research is needed regarding: Pharmacist Only triptans use by migraineurs currently using over-the-counter medicines and non-migraineurs; the efficacy of triptans; and the risk of cardiovascular AEs, cerebrovascular AEs, and chronic headache with triptans.

Down-scheduling the oral contraceptive pill (OCP)

The second case study applies the economic evaluation framework to estimate the cost-effectiveness of down-scheduling the OCP from prescription only (Schedule 4) to Pharmacist Only (Schedule 3) in Australia.

The OCP is a highly effective and widely used birth control method. However, the OCP is only available via prescription in Australia, even if the patient has used the OCP regularly and has not experienced any adverse events. Studies have found that the requirement to obtain a prescription is a barrier to women initiating and continuing using the OCP. As a result, women may use a less effective contraceptive, such as the rhythm method, or no contraceptive at all.

Unintended pregnancy may result from not using contraception. It may also result from the choice of a less effective contraceptive method or from poor compliance. Unintended pregnancies may result in a live birth, miscarriage, stillbirth, ectopic pregnancy or an abortion. These outcomes may lead to poorer maternal and child health outcomes and additional healthcare resource use.

Down-scheduling the OCP would remove some barriers to treatment, thereby potentially increasing the use of contraceptives and reducing discontinuation rates. Both these outcomes are expected to reduce unintended pregnancies, thereby generating better health outcomes and improving resource use. However, there are several risks from down-scheduling OCPs in terms of adverse events. Furthermore, some patients may substitute condoms for OCPs, thus increasing their risk of sexually transmitted infections (STIs).

A Markov model was used to synthesise data from a variety of sources. Behaviour before down-scheduling was estimated using data from the Household, Income and Labour Dynamics in Australia (HILDA) survey, while behaviour after down-scheduling was estimated using survey data.

Health outcomes included pregnancies, pregnancy outcomes (live birth, miscarriage, stillbirth, ectopic pregnancy, abortion and death), STIs, adverse events (venous thromboembolism (VTE), depression, myocardial infarction and stroke), ovarian cancer cases and QALYs. Costs included those related to GP and specialist consultations, contraceptives and other medicines, pharmacist time, hospitalisations and adverse events.

Overall, it was predicted that down-scheduling the OCP will result in a net health gain of 20,031 QALYs gained and $3,956 million saved over 35 years. Thus down-scheduling OCPs will be more effective and cost-saving. However, sensitivity analysis found that more research regarding the probability of pregnancy in women not using contraception and not trying to conceive is needed.

***Conclusion***

The case studies demonstrate that it is possible to apply an economic evaluation approach to scheduling decisions. They also illustrate the advantages of the approach, and identify several limitations. Finally, they illustrate that the approach can provide decision makers with new insights that they may not have been aware of otherwise.

The results of any economic evaluation should not be considered in isolation, but as a part of the broader body of evidence regarding the types of health impacts, the extent of the available evidence, who will be affected, and the role of medical practitioners and pharmacists in mitigating any risks. It could also be used in conjunction with the Brass framework.

Ultimately this report aims to start a conversation and encourage decision makers to consider a more innovative approach to down-scheduling decisions, and thus maximise the health of the Australian population.

# 1. Introduction

**Synopsis**

Australia spent $161.6 billion on healthcare in 2014–15, which accounted for 10.0% of GDP.[1, 2] Expenditure on medicines represented around 12.3% ($19.8 billion) of all healthcare spending. While the majority of medicines used to treat Australians require a prescription, medicines used for self-medication represented 26% of the total expenditure on medicines in Australia in 2016.[3] Most Australians have self-medicated in the past year with OTC medicines and complementary medicines.[4]

Initially patients require a prescription to access most new medicines. Decision makers may later 'switch' or 'down-schedule' these medicines to being available OTC. The current regulatory environment that determines the level of access to medicines in Australia and whether a prescription is required is described in this section. The interaction of this current regulatory environment with other regulatory mechanisms that influence access is also outlined, such as listing on the Pharmaceutical Benefits Scheme (Australia's list of Government-subsidised medicines), prescribing by nurse practitioners, emergency supply by pharmacists, and direct to consumer advertising.

Research suggests that while Australia was previously active in down-scheduling medicines compared to the rest of the world, in recent years Australia has adopted a more conservative approach.[7] In Australia, decision makers have been largely focusing on patient risk when making decisions about whether to restrict a medicine to prescription only or allow it to be available OTC (also known as scheduling decisions).[6] However, there are a wide range of benefits to the patient and the healthcare system from allowing a medicine to be available OTC. Decision makers in Australia may already consider these benefits, although they may be given less importance as they are not included in the formal list of factors to be considered.[6]

An external review of medicines and medical devices regulation was conducted for the Australian Federal Minister for Health in 2015.[8] The review recommended that the framework used to determine scheduling decisions be reviewed and suggested that a formal risk-benefit framework may assist. This section argues that there are several advantages to applying an economic evaluation approach to assess whether a medicine should be down-scheduled from prescription only (Schedule 4 in Australia) to Pharmacist Only (Schedule 3 in Australia), and vice versa.

Australia spent $161.6 billion on health in 2014–15, including expenditure by the Commonwealth and State Governments, private health insurance, individuals and non-government organisations.[1, 2] This accounted for 10.0% of GDP. Expenditure on medicines represented around 12.3% ($19.8 billion) of all health spending. While the majority of medicines used to treat Australians require a prescription, medicines used for self-medication represented 26% of the total expenditure on medicines in Australia in 2016.[3] Medicines used for self-medication are those available to the consumer without a prescription. This includes both OTC medicines and complementary medicines.

OTC medicines include treatments for coughs and colds, allergies, minor pain, skin conditions, fungal infections, acid reflux etc. Complementary medicines are medicinal products which contain ingredients such as herbs, vitamins, minerals, nutritional supplements, homeopathic and aromatherapy preparations. Traditionally, medicines suitable for OTC:

- treat a self-diagnosable condition, and there are minimal consequences from misdiagnosis;

- have mild side-effects that are also self-diagnosable;
- have minimal potential harm in the case of accidental or intentional misuse; and
- are not addictive.[23, 24]

However, some OTC medicines are used to treat long-term conditions or for prevention,[7] or where a previous medical diagnosis,[25] or pharmacist-aided diagnosis[26] have occurred.

A complementary medicine is defined by the *Therapeutic Goods Regulations 1990 Act* as "a therapeutic good consisting principally of one or more designated active ingredients mentioned in Schedule 14 of the Regulations, each of which has a clearly established identity and traditional use".[27]

Most Australians use OTC medicines for multiple reasons, including prevention and symptomatic relief, and complementary medicines to maintain or improve their overall health. For example, a recent study found that 83.1% and 96.6% of Australians had used an OTC medicine in the past month and year, respectively, and 70% had used vitamins, minerals or supplements in the past year (N=1,146).[4]

Some medicines that are initially available as prescription only are later made available OTC. 'Switching' or 'down-scheduling' a medicine from prescription only to being available OTC may be beneficial for patients and the healthcare system in terms of improved health outcomes and reduced healthcare resource use. However, there are also risks to down-scheduling a medicine. Whether the benefits of down-scheduling a medicine to being available OTC outweigh the risks largely depends on the medicine under consideration. The next section discusses how decision makers currently make these decisions in Australia.

# 1.1. The current regulatory environment

## 1.1.1. Australian Register of Therapeutic Goods

OTC medicines and complementary medicines must be registered or listed on the *Australian Register of Therapeutic Goods (ARTG),* which is regulated by the Therapeutic Goods Administration (TGA). Listed medicines (AUST L) are those considered to be low-risk, and contain pre-approved, low-risk ingredients and make limited claims, while registered medicines (AUST R) are those considered to be higher risk. Most OTC medicines and all prescription medicines are registered on the ARTG, while most complementary medicines are listed on the ARTG – although some are registered. Both registered and listed medicines are assessed by the TGA for quality and safety, however registered medicines are also assessed for efficacy.[28]

## 1.1.2. The Poisons Standard

In Australia, the *Poisons Standard* sets out the degree of control over the availability of medicines and poisons to the public.[5] These restrictions are then implemented through the relevant State and Territory legislation. The *Poisons Standard* contains the Standard for the Uniform Scheduling of Medicines and Poisons (abbreviated SUSMP). The SUSMP classifies substances into ten different Schedules, although Schedule 1 is not currently used (see Table 1-1). Prescription only medicines are listed under Schedule 4 and 8, while OTC medicines are listed under Schedule 2 and 3:[5, 29]

- Schedule 3 (Pharmacist Only): These medicines are available behind the pharmacy counter. A pharmacist must be consulted before dispensing.

- Schedule 2 (Pharmacy Medicine): These medicines may be available on the shelf at pharmacies. If required, advice from a pharmacist or pharmacy assistant should be available.

In addition, some medicines are exempt from scheduling (or are "unscheduled"), and thus are not listed on the SUSMP. These medicines are available in pharmacies but are also available through other distributional channels, such as supermarkets, online stores and health food stores.

A medical practitioner may write a prescription for unscheduled, Schedule 2 and 3 medicine, but a prescription is not required to access these medicines. However, patients must have a prescription written by a medical practitioner to access Schedule 4 (prescription only) and Schedule 8 (controlled drugs) medicines.

**Table 1-1: The Standard for the Uniform Scheduling of Medicines and Poisons**

| Schedule | Description | | Examples |
|---|---|---|---|
| Schedule 1 | Not currently in use | | |
| Schedule 2 | Pharmacy Medicine | Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person. | Aspirin, paracetamol or ibuprofen |
| Schedule 3 | Pharmacist Only Medicine | Substances, the safe use of which requires professional advice but which should be available to the public from a pharmacist without a prescription. | Chloramphenicol (for ophthalmic use), pseudoephedrine |
| Schedule 4 | Prescription Only Medicine OR Prescription Animal Remedy | Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription. | Amoxycillin, simvastatin, sumatriptan |
| Schedule 5 | Caution | Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label. | Acetone |
| Schedule 6 | Poison | Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label. | Hydrochloric acid |
| Schedule 7 | Dangerous Poison | Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply. | Arsenic, cyanides |
| Schedule 8 | Controlled Drug | Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence. | Oxycodone, morphine |
| Schedule 9 | Prohibited Substance | Substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities. | Heroin, lysergic acid (LSD), 3,4-methylenedioxy-amphetamine (MDMA) |

| Schedule | | Description | Examples |
|---|---|---|---|
| Schedule 10 | Substances of such danger to health as to warrant prohibition of sale, supply and use | Substances which are prohibited for the purpose or purposes listed for each poison. | Amygdalin (for therapeutic use) |

Source: [5]

### 1.1.3. Factors currently influencing scheduling decisions

Since 1 July 2010 the Advisory Committee of Medicines Scheduling (ACMS), an expert advisory committee of the TGA, considers scheduling proposals and provides advice to the delegate of the Secretary of the Department of Health regarding the schedule which a substance should be listed on the *Poisons Standard*. The ACMS comprises of nine representatives of the Federal and State Governments, and up to six independent experts.[30, 31] The final decision is made by a delegate of the Secretary of the Department of Health.

Most medicines are first listed under Schedule 4 (prescription only) or Schedule 8 (controlled). Thus initially patients require a prescription to access most new medicines. Some medicines may be later assessed for whether they are suitable for down-scheduling to Schedule 3 (Pharmacist Only), 2 (pharmacy medicine) or unscheduled after an application for down-scheduling is submitted for consideration. This may not occur for many years when enough evidence is accumulated regarding, for example, the risk of adverse events, and whether the condition and adverse events are self-diagnosable and self-manageable.

The benefits and risks of different levels of access to substances are considered by the ACMS when making scheduling decisions. The Scheduling Policy Framework for Medicines and Chemicals outlines the specific factors that should be considered for therapeutic goods.[6] Details of the factors considered are provided in Table 1-2.

Scheduling decisions are made using the “cascading principal”. For medicines, a substance is first assessed using the factors for Schedule 8. If the factors for Schedule 8 are not applicable, the substance is assessed against the Schedule 4 factors and if not applicable, against the Schedule 3 factors, and if not applicable, against the Schedule 2 factors.[6]

The factors considered by the ACMS largely focus on patient risk. Increasing access to a medicine by listing it on a lower schedule may reduce the proportion of patients seeking advice from a medical practitioner or pharmacist. Depending on the condition, reduced medical oversight may increase the risk of inaccurate or delayed diagnosis (including from opportunistic screening), and inappropriate use. Increased use of a medicine may also increase the incidence or severity of some adverse events, especially for patients with co-morbidities or those using other medicines. Thus listing a medicine on a lower schedule may result in suboptimal health outcomes.

However, there are also benefits to the patient and the healthcare system from listing a medicine on a lower schedule. It may improve patient health outcomes by reducing barriers to treatment. This may reduce the time to symptom relief, and improve treatment rates and adherence. Reducing barriers to treatment may also encourage patients to switch to more effective or safer treatments. Consequently, health-related quality of life may be improved, the onset of related diseases may be prevented, and disease progression may be delayed. Down-scheduling a medicine may reduce GP attendances for common conditions. Furthermore, improved health outcomes may lead to less demand for healthcare, such as diagnostic tests and hospitalisations. These resources could be used to treat and diagnose other patients. Thus down-scheduling could reduce the pressure on Government budgets. Overall, whether the benefits

of down-scheduling a medicine to being available OTC outweigh the risks largely depends on the medicine under consideration.

The Committee may consider these benefits, although they may be given less importance as they are not included in the Scheduling Policy Framework for Medicines and Chemicals (see Table 1-2).

**Table 1-2: Factors considered by the Advisory Committee of Medicines Scheduling**

| Schedule | Factors considered |
|---|---|
| Schedule 2 | 1. The quality use of the medicine can be achieved by labelling, packaging, and/or provision of other information; however access to advice from a pharmacist is available to maximise the safe use of the medicine.<br>• The medicine is for minor ailments or symptoms that can easily be recognised and are unlikely to be confused by the consumer with other more serious diseases or conditions. Treatment can be managed by the consumer without the need for medical intervention. However, the availability of a pharmacist at the point of sale supports the consumer in selecting and using the appropriate medicine.<br>2. The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low.<br>• Suitable for diagnosis and treatment by the consumer in the management of minor ailments.<br>3. The use of the medicine at established therapeutic dosage levels is unlikely to produce dependency and the medicine is unlikely to be misused, abused or illicitly used.<br>4. The risk profile of the medicine is well defined and the risk factors can be identified and managed by a consumer through appropriate packaging and labelling and consultation with a medical practitioner if required.<br>• There is a low and well-characterised incidence of adverse effects; interactions with commonly used substances or food and contraindications.<br>5. The use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition.<br>• Appropriate labelling and packaging can manage any risks. |
| Schedule 3 | 1. The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately.<br>• The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use. Pharmacist-consumer dialogue is necessary to reinforce and/or expand on aspects of the safe use of the medicine.<br>2. The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by a pharmacist.<br>3. The risk profile of the medicine is well defined and the risk factors for adverse effects and interactions are known, identifiable and manageable by a pharmacist.<br>4. Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or a pharmacist.<br>• The consumer may not be able to self-monitor the safe ongoing use of the medicine. The condition does not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management.<br>5. The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition.<br>• Pharmacist-consumer dialogue is required to detect the risk of masking a serious disease or compromising medical management of a disease, and to deal with it appropriately. |
| Schedule 4 | 1. The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention<br>• Diagnosis, management or monitoring of the medical condition is such that it requires medical, veterinary or dental intervention before the substance is used.<br>2. The use of the substance requires adjunctive therapy or evaluation. |

| Schedule | Factors considered |
|---|---|
| | • Adjunctive therapy could include other medicines, non-pharmacological measures, or specialised medicine delivery devices. Evaluation could include laboratory tests or additional clinical assessments.<br>3. The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use.<br>• Control of access and duration of therapy by a medical, veterinary or dental practitioner is required.<br>4. The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance.<br>5. The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical, veterinary or dental intervention to minimise the risk of using the substance.<br>6. The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical, veterinary or dental practitioner.<br>7. The use of the substance has contributed to, or is likely to contribute to, communal harm.<br>• For example the development of resistant strains of microorganisms. Appropriate use, and/or the decision to continue treatment, requires evaluation by a medical, veterinary or dental practitioner.<br>8. The experience of the use of the substance under normal clinical conditions is limited.<br>• Unexpected effects of the substance may only become evident after widespread use. Close monitoring of the patient is required by a medical, veterinary or dental practitioner to monitor for unanticipated effects. |
| Schedule 8 | 1. The substance is included in Schedule I or II of the United Nations Single Convention on Narcotic Drugs 1961 or in Schedule II or III of the United Nations Convention on Psychotropic Substances 1971.<br>2. The substance has an established therapeutic value but its use, at established therapeutic dosage levels, is recognised to produce dependency and has a high propensity for misuse, abuse or illicit use.<br>3. The substance has an established therapeutic value but by reason of its novelty or properties carries a substantially increased risk of producing dependency, misuse, abuse or illicit use. |

Source: [6]

Gauld et al (2014) analysed down-scheduling of prescription to OTC medicines across six countries.[7] The authors found that Australia was initially active in down-scheduling medicines compared to the rest of the world, however in recent years Australia has adopted a more conservative approach (see Table 1-3). More recently, New Zealand down-scheduled sildenafil for the treatment of erectile dysfunction in 2014 and in January 2017 Medsafe recommended down-scheduling OCPs.[32-34]

Since the 1990s, Australia and New Zealand have been attempting to harmonise the scheduling of medicines.[35] This was formalised in September 2003, when the Governments of both countries signed a treaty agreeing to establish a joint scheme for the regulation of therapeutic products.[36] This was referred to as Australia New Zealand Therapeutic Products Agency. On 20 June 2011 a 'Statement of Intent' was signed, reaffirming the commitment.[36] However on 20 November 2014 the Governments of both countries announced that they would cease efforts to establish the Australia New Zealand Therapeutic Products Agency, following a review of progress and the assessment of the costs and benefits.[37] It is clear from Table 1-3 the treaty had limited success.

Gauld et al (2015) conducted and analysed interviews with 27 key participants to explore the reason for differences in the rate of down-scheduling in Australia compared to New Zealand.[35] The authors found that Australian industry, pharmacy and committee member participants commonly described the committee and regulator as risk-averse (although medical and consumer participants did not). Some participants also suggested that the committee lacked confidence in Australian pharmacy services. Of particular concern, some participants suggested that decision making was sometimes not evidence-based,

due to large workloads, inadequate preparation, the regulator's influence and the nature of the membership.

The authors also found a variety of other barriers to down-scheduling in Australia, including the impact of advertising restrictions, immediate generic entry and pharmacy house-brands on the willingness for industry to apply for down-scheduling. While these interviews were conducted before there was extensive experience with the new ACMS (implemented in 2010), subsequent decisions regarding down-scheduling suggests that the risk-aversion has remained.

**Table 1-3: Comparison of timing of down-scheduling decisions across countries up to and including 2013**

| Drug | UK | New Zealand | Australia | Netherlands | US | Japan |
|---|---|---|---|---|---|---|
| Inhaled short-acting beta agonist | X | X | 1976[a] | X | X[b] | X |
| Urinary bladder spasm treatment (flavoxate) | X | <1990[c] | <1990[c] | X | X | 2007 |
| Non-sedating antihistamine | 1983[d] | <1990 | ≤1992 | ≤1995 | 2002 | 1990 |
| Ibuprofen | 1983 | 1985 | 1989 | ~1987 | 1984 | 1985 |
| Naproxen | 2008 | ≤1990 | 1983[a] | 1996 | 1994 | X |
| Dermal hydrocortisone 1% | 1987 | 1990 | ~1997 | X | 1991 | X[e] |
| Nicotine replacement (any form) | 1991 | <1990 | 1988[a] | ~1992 | 1996 | 2001 |
| Vaginal azole antifungal | 1992 | 1990 | 1994 | 2011 | 1990 | 2007 |
| Dermal nucleoside analogue (e.g. aciclovir) | 1993 | 1990 | 1996 | ≤2000 | X | 2007 |
| Nasal corticosteroid | 1994 | 1996 | 1999 | X | 2013 | 2010 |
| H2-antagonist | 1994 | 1993 | 1995 | ≤1996 | 1995 | 1997 |
| Steroid for local oral use | 1994 | 1991 | 1996 | X | X | 2006 |
| Mast cell stabilizer (any form) | 1994 | 1991 | <1990 | ≤1995 | 1997 | 1996 |
| Azole antifungal (oral, single dose) | 1995 | 2004 | 2003 | X | X | X |
| Mebeverine | 1997 | X | X | X | X | X |
| Domperidone | 1998 | X | X | <1991 | X | X |
| Dermal moderate potency corticosteroid | 2001 | 2005 | 2000 | X | X | X |
| Orlistat | 2009 | 2004 | 2004 | 2009 | 2007 | X |
| Proton pump inhibitor | 2003 | 2008 | 2005 | 2008 | 2003 | X |
| Emergency hormonal contraception | 2001 | 2001 | 2003 | 2005 | 2006 | X |
| Statin | 2004 | X | X | X | X | X |
| Ocular chloramphenicol | 2005 | 2009[f] | 2010[f] | X | X[f] | X[f] |
| Triptan | 2006 | 2006 | X | X | X | X |
| Neuraminidase inhibitor (oseltamivir) | X | 2006 | X | X | X | X |
| Chlamydia treatment (azithromycin) | 2008 | X | X | X | X | X |
| Alpha-1 blocker (tamsulosin) | 2009 | X | X | X | X | X |
| Oral antiviral for herpes labialis | X | 2009 | 2011 | X | X | X |
| Tranexamic acid | 2010 | X | X[g] | X | X | 2007[h] |
| Dermal calcipotriol | X | 2010 | X | X | X | X |
| Cholera and travellers' diarrhoea vaccine | X | 2011 | X | X | X | X |
| Influenza vaccination | X | 2012 | X[i] | X | X | X |

| Drug | UK | New Zealand | Australia | Netherlands | US | Japan |
|---|---|---|---|---|---|---|
| Trimethoprim | X | 2012 | X | X | X | X |
| Transdermal oxybutynin | X | X[j] | X | X | 2013 | X |
| Meningococcal vaccine | X | 2013 | X | X | X | X |
| Tetanus-diphtheria-pertussis vaccine | X | 2013 | X | X | X | X |
| Herpes zoster vaccine | X | 2013 | X | X | X | X |
| Sildenafil | X | 2014 | X | X | X | X |
| Adapalene topical | X | 2016 | X | X | 2016 | X |
| Oral contraceptive pill | X | 2017 | X | X | X | X |

**X** = not down-scheduled.
a. Timing of early Australian down-scheduling decisions differed between the States and Territories. The earliest down-scheduled date is shown.
b. Orciprenaline (metaproterenol), a non-selective beta-agonist was down-scheduled in the US in 1982, but reversed in 1983.
c. Flavoxate is nonprescription in both Australia and New Zealand, but marketed in neither.
d. The non-sedating antihistamine down-scheduled in the UK in 1983 was terfenadine, which later reverted to prescription medicine following QT prolongation concerns.
e. Hydrocortisone 1% with oxytetracycline (but not alone) has long been available without prescription in Japan.
f. Other antibacterial eye preparations have long been available without prescription in these jurisdictions, e.g. sulfacetamide in New Zealand and Australia, polymyxin and bacitracin in the US, and sulfamethoxazole in Japan.
g. Tranexamic acid was down-scheduled in Australia in 2000 but never marketed as a nonprescription medicine and reverted to prescription in 2007 under Trans-Tasman Harmonization.
h. Tranexamic acid in Japan was down-scheduled at a lower dose, in combination with other ingredients, and for a different indication to the UK (chloasma not menorrhagia).
i. May be administered by a pharmacist without a prescription in some states of Australia.
j. Oral oxybutynin was previously available without prescription in New Zealand.
Note: Medicines are oral unless otherwise specified. All vaccines are injected except for the cholera and travellers' diarrhoea vaccine which is oral.
Source: [7, 32, 33, 38]

## 1.1.4. Other regulatory factors affecting access to medicines in Australia

### *1.1.4.1. The Pharmaceutical Benefits Scheme*

Evidence suggests the cost of medicines can create financial barriers, and thus affect the use of medicines by patients.[39]

In Australia, medicines listed on the PBS or Repatriation Pharmaceutical Benefits Scheme (RPBS) schedules are eligible for public subsidy. In general, medicines prescribed by medical practitioners out of hospital and dispensed at community pharmacies listed on the PBS or RPBS are covered, however some medicines dispensed at public hospitals or specialist treatment centres are also covered by the PBS (i.e. Section 100 medicines). A patient cannot receive PBS or RPBS subsidy without a prescription written on a PBS or RPBS prescription form. Some Schedule 2 and 3 medicines are listed on the PBS or RPBS and thus are eligible for public subsidy, however most are not and so patients must pay for these medicines out-of-pocket.

Most Schedule 2 and 3 medicines listed on the PBS or RPBS are restricted to certain populations. For example, paracetamol is available in various forms for Aboriginal and Torres Strait Islanders, palliative care, and veterans (for RPBS medicines).[40] Furthermore, some Schedule 2 and 3 medicines are available at higher doses via prescription only (Schedule 4) and are listed on the PBS. For example, diclofenac tablets are available OTC if the dosage is 25 mg or less and the pack size is 30 or less, but diclofenac 50 mg is available via prescription only and is listed on the PBS for:

- patients with chronic arthropathies (including osteoarthritis), with an inflammatory component;
- patients with bone pain due to a malignant disease; and

- patients with severe pain receiving palliative care.[5, 40]

Finally, some Schedule 2 and 3 medicines are available in larger pack sizes via prescription only (Schedule 4) and are listed on the PBS. For example, 14 tablets of ranitidine 150 mg are available OTC, but 60 tablets of ranitidine 150 mg are available as prescription only and are listed on the PBS.[5, 40]

As a patient cannot receive a PBS subsidised medicine without a prescription, the financial cost to a patient may be lower if they received a prescription for a Schedule 2 or 3 medicine rather than going directly to a pharmacy, despite the total cost of the medicine being higher. As a result, even if a medicine is down-scheduled some patients may be unwilling to buy the medicine OTC. For example, up until January 2016 Mylanta (aluminium hydroxide with magnesium hydroxide, oral suspension 200 mg-200 mg per 5 mL, 500 mL) was available on the PBS (PBS item: 2157M). Box 1-1 outlines the costs that would have been paid by the patient if they obtained the medicine OTC compared to via a PBS prescription.

**Box 1-1: Example of costs of OTC medicines if PBS subsidised versus not**

**Mylanta: aluminium hydroxide with magnesium hydroxide, oral suspension 200 mg-200 mg per 5 mL, 500 mL, December 2015**

In December 2015 the PBS dispensed price for maximum quantity for Mylanta was $20.23.[41] If the patient was a concessional card holder, the patient would have paid a $6.10 co-payment and the Government would have paid $14.13 (unless the patient had reached the safety net, in which case they would have paid nothing and the Government would have paid $20.23).[42] However, if the patient purchased Mylanta OTC at a pharmacy, the patient would have paid around $6.99.[43]

Note that the co-payment for non-concession card holders was $38.30.[42] As this is higher than the cost of Mylanta at the pharmacy (around $6.99), it would not have been subsidised by the PBS and the patient would have likely to have paid $6.99.[43]

Note: the co-payment for non-concession card holders was $38.30.[42]As this is higher than the cost of Mylanta at the pharmacy (around $6.99), it would not have been subsidised by the PBS and the patient would have paid $6.99.[43]

In recognition of price discrepancies, and to reduce the pressure on the PBS budget, the Commonwealth Government de-listed several OTC medicines from the PBS in the 1997-98 budget.[44] These included:

- medicines for the treatment of common gastro-intestinal problems;
- an anti-inflammatory liniment for pain relief of sprains and muscle strains;
- a number of preparations that used to be compounded by pharmacists, but which are now mostly being supplied in a pre-packaged form by manufacturers; and
- two prescription antifungal products.[44]

More recently, the Commonwealth Government de-listed 17 OTC medicines from the PBS in January 2016, including Mylanta (aluminium hydroxide with magnesium hydroxide), aspirin, hydrocortisone, folic acid and paracetamol.[45]

Note that the decision to de-list a medicine from the PBS is separate from the decision to down-schedule a medicine.

#### *1.1.4.2. Prescribing exceptions*

There are some exceptions to the rule that a medical practitioner must write a prescription for a patient to access a Schedule 4 or 8 medicine. These exceptions vary by States and Territories.

Emergency supply by pharmacists on direction of a medical practitioner: In some States and Territories it is possible for a prescription to be provided by the medical practitioner to a pharmacist orally, by telephone, by electronic mail or by facsimile, if the written prescription is immediately written and sent to the pharmacist.[46]

Emergency supply by pharmacists not on direction of a medical practitioner: In some States and Territories it is possible for pharmacists to supply a small amount of a Schedule 4 or 8 medicine without a prescription in emergency situations. For example, in New South Wales a pharmacist may supply a patient with three days' worth of treatment of a Schedule 4 or 8 medicine if:[46]

(a) that the person is undergoing treatment essential to the person's well-being, and

(b) that the substance has previously been prescribed for the treatment, and

(c) that the person is in immediate need of the substance for continuation of the treatment, and

(d) that, in the circumstances, it is not practicable for the person to obtain a prescription for the substance from an authorised practitioner.

Supply of influenza vaccine: In some States and Territories pharmacists may administer the influenza vaccine without a prescription from a medical practitioner, conditional on the pharmacist completing an accredited training course.[46]

Continued dispensing: Under the *National Health (Continued Dispensing) Determination 2012* pharmacists may supply a standard amount of some PBS-subsidised HMG-CoA reductase inhibitors (statins) and OCPs under the following circumstances:[47, 48]

(a) The medicine requested is eligible for supply by Continued Dispensing (e.g. PBS-subsidised, not authority required).

(b) There is an immediate need for supply of the medicine to facilitate continuity of therapy, and it is not practicable for the patient to obtain a prescription for the medicine from an authorised prescriber.

(c) The medicine has been previously prescribed to the patient.

(d) The patient's therapy is stable (e.g. no recent change to dose or dosing regimen, the patient has been taking the medicine for an uninterrupted period).

(e) There has been prior clinical review by the prescriber that supports continuation of the medicine (e.g. there has been a consultation with the prescriber in the past twelve months).

(f) The patient had a valid prescription the last time the medicine was supplied.

(g) The medicine requested has not been supplied under Continued Dispensing in the past twelve months.

Finally, some authorised nurse practitioners may prescribe a limited number of PBS medicines. Nurse practitioners are registered nurses who are endorsed by the Nursing and Midwifery Board of Australia to function autonomously and collaboratively in an advanced and extended clinical role, on the basis of advanced practice nursing experience and approved educational qualifications at master's level or equivalent.[49] In September 2012 there were 765 nurse practitioners in Australia.[49] They primarily worked in adult emergency care (32%), chronic disease management (15%), acute nonemergency care (14%) and primary care/general practice (10%), especially in isolated communities.[49, 50]

#### 1.1.4.3. Scheduling and direct to consumer advertising

Direct to consumer advertising of OTC medicines may also affect their use. In Australia, unscheduled and pharmacy medicines (Schedule 2) can be advertised directly to consumers. On the other hand,

prescription medicines (Schedule 4 and 8) can only be advertised to health professionals (e.g. through medical journals) under Section 42DL of the *Therapeutic Goods Act 1989, and* Schedule 3 cannot be advertised directly to consumers unless they are listed in Appendix H of the Poisons Standard.[27]

Prior approval may be required for certain types of advertisements aimed at consumers. These include advertisements on television, radio and in newspapers. The Secretary of the Department of Health or his/her delegate is responsible for approving these advertisements. Under co-regulatory arrangements, this responsibility has been delegated to industry associations (Australian Self-Medication Industry and Complementary Healthcare Council).[51] All applications to advertise pharmacist only (Schedule 3) medicines have been rejected since 2007, citing no "public benefit".[35]

Direct to consumer advertising is controversial. Proponents for advertising argue that advertising raises patient awareness of diseases and treatment options, improve patient-doctor communication, improve adherence and ultimately health outcomes.[52-54] For example, pharmacists interviewed by Chaar and Kwong (2010) reported that advertising of OTC medicines may prompt certain groups who typically disregard their symptoms or are embarrassed to seek advice.[54] On the other hand, opponents argue that advertisements are not unbiased sources of information, may result in inappropriate demand for medicines, and medical practitioners or pharmacists may feel pressure to supply medicines.[52-54] Pharmacists interviewed by Chaar and Kwong (2010) reported that they must spend additional time persuading patients from purchasing an inappropriate medicine and if conflict arises, a patient may choose to go to another pharmacy.[54]

There is limited high quality evidence regarding the impact of direct to consumer advertising on patient, medical practitioner and pharmacist behaviour.[52]

Regarding prescription medicines, Mintzes et al (2003) surveyed medical practitioners in Canada and the US and found that direct to consumer advertising increases patient requests for specific medicines[55], while McKinlay et al (2014) used a randomised experimental design and found that patient requests for specific medicines resulted in an increased probability of the medicine being prescribed.[56] There is mixed evidence about the impact of direct to consumer advertising on adherence to prescription medicines. Calfee et al (2003) analysed observational data before and after the FDA eased advertising restrictions and found that direct to consumer advertising increased compliance to statins.[57] On the other hand, Green (2017) found that direct to consumer advertising reduced adherence among patients with serious mental illness, often because of side effect information in advertisements.[58] Finally, Daubresse et al (2015) analysed observational data regarding sales of asthma medicines and found that advertising increased pharmacy sales, significantly increased emergency room visits, but did not have a significant impact on hospitalisations or outpatient encounters.[59]

Regarding Pharmacist Only medicines, Zhao (2016) used a discrete choice experiment to explore the impact of advertising on patients and pharmacists.[60] The study found that advertising increased the likelihood that patients would seek treatment from a pharmacist, rather than a GP, and were more likely to use the advertised product. However, the study found that the advertisement did not have a significant impact on the recommendations made by pharmacists.

There has been no studies on the impact of direct to consumer advertising on health outcomes.[52]

# 1.2. Proposed changes to the regulatory environment

## 1.2.1. Review of medicines and medical devices regulation

An external review of medicines and medical devices regulation was conducted for the Australian Federal Minister for Health in 2015.[8] One consideration was the current approach to scheduling and re-scheduling decisions. The review noted that a formalised methodology for assessing benefits and risks to inform scheduling decisions had merit due to three main reasons. It would:

- facilitate a structured and systematic approach, ensuring that multiple domains of benefits and risks are explored and promote consistency of decision making;
- increase transparency, making it easier for sponsors to frame a case for re-scheduling, or other interested parties to input to the process; and
- make the formulation of recommendations and/or statements of reason for a decision easier, and provide a consistent format to such documents, making them easy to read, digest and understand.

The external review of medicines and medical devices regulation recommended that:

> *...the Scheduling Policy Framework be reviewed, in consultation with State and Territory Governments to provide for the development and adoption of a formal risk-benefit methodology to assess scheduling applications, and opportunities to enhance input from interested parties into the scheduling process (Recommendation 11).*

While the review did not recommend a specific formal risk-benefit methodology, it noted that a potential approach has been proposed by Brass et al (2011).[9]

The Australian Government has since accepted this recommendation, but also noted that the Australian Health Ministers Advisory Council has overall policy responsibility for the Scheduling Policy Framework, and therefore would need to consider any proposed changes.[61]

## 1.2.2. The Brass framework

Brass et al (2011) developed a benefit-risk assessment framework for non-prescription medicines.[9] The authors proposed a modified value-tree framework to identify important benefit and risk attributes.[9] The authors identified several major, broad benefit and risk domains that are often considered by decision makers when assessing an OTC medicine. Economic benefits were included as a potential benefit domain, such as reduced medical practitioner consultations, however the authors note that these are not typically a regulatory consideration. Application of the value-tree framework involves identifying the product-specific benefit or risk attributes under each major domain. Not all medicines will have an attribute relevant to each domain, or alternatively may have several relevant attributes.

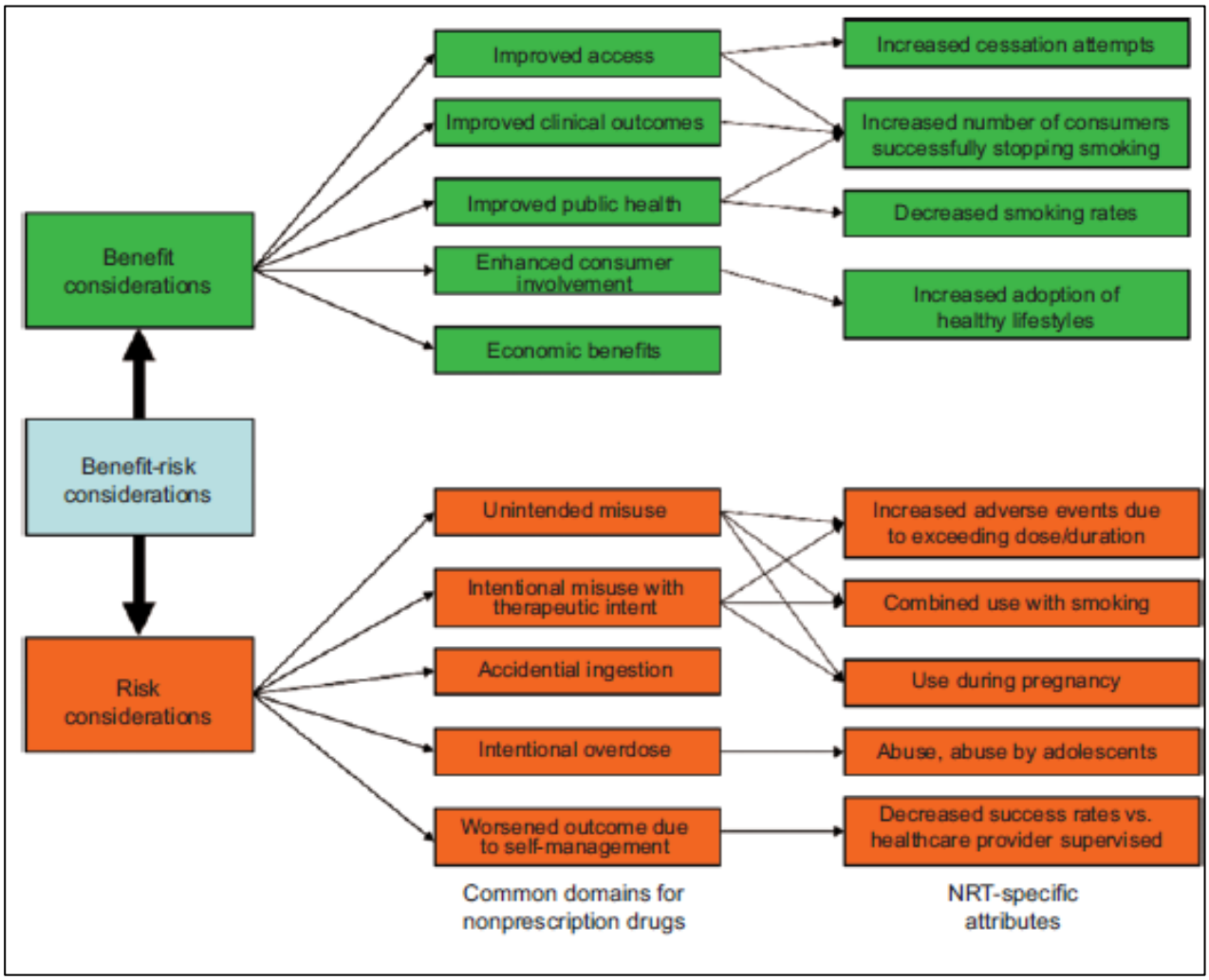
The authors then propose the application of the International Risk Governance Council Framework and Multiple Criteria Analysis (MCA) to guide the overall evaluation process.[9] In particular, the authors suggest that the MCA stage involves the following three steps.[9]

1. Calibrating the existing data on each attribute identified in the value-tree process. This can be done in terms of, for example, a utility transformation on a scale from zero (no effect) to 100 (extremely high effect). For a nonprescription medicine, the numerical value may reflect the magnitude of the clinical sequelae, either benefit or risk, associated with each attribute.

2. Multiplying these scale values with the probability of their likelihood to obtain a more accurate impact value.
3. Assigning relative importance weights to each of the criteria (trade-offs). Trade-offs determine the relative importance of one criteria compared to that of any of the other criteria. They normally range from zero to one, and must always add up to one.

An example application of the value-tree method to identify the benefits and risks of scheduling of nicotine replacement therapies is provided in Figure 1-1 and Table 1-4. The frequency and clinical impact of each attribute are given a numerical value between zero and three. For frequency, zero reflects a behaviour that almost never occurs, while three reflects a high frequency. For the clinical impact, zero reflects an event that has no clinical impact and three reflects the event has a high clinical importance. The overall attribute score is calculated as the product of the attribute's frequency and importance scores.[62] The authors propose that a Group Delphi method could be used to allocate scores.[62]

**Figure 1-1: Example application of the value-tree methods to nicotine replacement therapies**




Source: [9]

**Table 1-4: Example application of the Brass approach to nicotine replacement therapies**

| | Frequency of behaviour | Clinical Impact | Overall score | Post marketing issues / plan |
|---|---|---|---|---|
| **Benefit attributes** | | | | |
| Increased smoking cessation attempts | 2 | 1 | 2 | |
| Increased number of consumers successfully stopping smoking | 2 | 3 | 6 | |
| Decreased smoking rates | 2 | 3 | 6 | |
| Increased adoption of healthy lifestyles | Unknown | Unknown | Unknown | Insufficient data to assess frequency or impact – no basis for assessing contribution to benefits |
| **Risk attributes** | | | | |
| Increased adverse events due to exceeding dose/duration | 1 | 1 | 1 | |
| Combined use with smoking | 2 | 1 | 2 | |
| Use during pregnancy | 2 | 1 | 2 | |
| Abuse by adolescents | Unknown | 1 | Unknown | |
| Decreased success rates vs healthcare provider supervised attempts | 0 | 3 | 0 | Insufficient data to permit assessment – post-marketing surveillance of abuse planned |

Source: [62]

Application of the Brass Framework can help manufacturers assess the likely success of an application for a medicine to be down-scheduled (early review), and thus can be used to screen medicines to identify potential candidates for down-scheduling. Application of the Brass Framework by both manufacturers and decision makers should also facilitate discussion about the benefits and risks of down-scheduling, ensure alignment on major issues, and enhance communication to patients.

### 1.2.3. The value of an economic evaluation approach

The Brass Framework can be extended to include an economic evaluation approach to inform scheduling decisions between Prescription Only (Schedule 4 in Australia) and Pharmacist Only (Schedule 3 in Australia). An economic evaluation approach provides several advantages over a MCA approach.

Economic modelling can be used to synthesise evidence from a variety of sources. This would enable decision makers to consider a broad range of benefits and risks, their likelihood of occurring and the magnitude of their impact on health outcomes and resource use. It could also be used to predict the overall expected impact of a scheduling decision on health outcomes and resource use before it occurs.

Aggregating the impact of scheduling decisions on a wide range of resource use, and thus costs, is relatively straight-forward. In contrast, it is more difficult to aggregate the impact of scheduling decisions on a wide range of different health outcomes, such as symptoms reduced or duration shortened, different diseases avoided, or the incidence and severity of different adverse events. Health outcomes can be aggregated to a single measure typically used in economic evaluations – QALYs, which incorporates life expectancy and quality of life, and is based on measures of the strength of patient or community preferences across these domains. QALYs are based on information regarding how the community trades-off different health outcomes, and thus avoid the need for decision makers to decide on the relative importance of each health outcome.

An economic evaluation approach includes the impact of scheduling decisions on healthcare resource use and costs. Healthcare resources are both valuable and scarce. Their use generates an opportunity cost because they could be used to treat other patients and reduce waiting times.

Scheduling decisions may improve or reduce overall health outcomes, and increase or decrease costs associated with healthcare resource use. If re-scheduling a medicine reduces health outcomes, then it is questionable whether the schedule change should go ahead. Alternatively, if re-scheduling improves health outcomes and decreases costs, then there is strong support for the schedule change. But the appropriate scheduling decision is less clear if re-scheduling a medicine improves health outcomes and increase costs. In this case, decision makers can use the ICER to assess whether the schedule change is 'value for money'.

Finally, sensitivity analyses can facilitate the assessment of whether uncertainty in the evidence results in uncertainty in the scheduling decision. It can enable decision makers to assess the importance of a certain parameter and whether re-scheduling should be delayed until further research is conducted. This avoids the risk of placing too much or too little importance on risks or benefits where the clinical impact or the frequency of events are unknown due to limited data. It can also enable decision makers to assess the impact of different regulatory decisions on health outcomes and resource use, and whether only a sub-group of patients should access a medicine OTC. Finally, probabilistic sensitivity analysis can estimate the probability that re-scheduling a medicine is cost-effective.

## 1.3. Summary

The Scheduling Policy Framework for Medicines and Chemicals outlines the factors that are currently considered by decision makers when making scheduling decisions in Australia.

However, an external review of medicines and medical devices regulation and several authors have identified the need for decision makers to consider all available evidence and that a formal risk-benefit methodology may assist.[7, 8, 35] Extension of the Brass Framework to include an economic evaluation approach can fulfil this need.

Currently an economic evaluation is required to form part of the evidence submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) in applications for medicines to be listed on the PBS, and cost-benefit analysis is recommended by the Office of Best Practice Regulation, Australian Government Department of the Prime Minster and Cabinet, to assess regulatory proposals.[19, 22] Thus applying an economic evaluation approach to inform scheduling decisions is consistent with existing government policy.

The rest of this report presents an economic evaluation framework to help inform decisions regarding whether a medicine should be listed on Schedule 4 (prescription only) or Schedule 3 (Pharmacist Only). The economic evaluation framework is an extension of the Brass framework[9], and is based on various guidelines currently available regarding how to conduct a health economic evaluation, or part thereof[10-22], however with some adjustment to focus it towards informing scheduling decisions.

The application of the economic evaluation framework is demonstrated using two case studies: down-scheduling triptans and down-scheduling the OCP.

# 2. An economic evaluation framework to inform the scheduling of medicines

**Synopsis**

This section presents an economic evaluation framework that could be used by sponsors and decision makers to inform scheduling decisions between Prescription Only (Schedule 4 in Australia) and Pharmacist Only (Schedule 3 in Australia). The economic evaluation framework is an extension of the Brass framework.[9]

There are several best practice guidelines already available regarding how to conduct a health economic evaluation, or part thereof.[10-22] The guidelines are generally well researched, supported by theory and backed by empirical research. These guidelines form the basis of the framework however with some adjustment to focus it towards informing scheduling decisions. In particular, the how patient behaviour changes can be considered within an economic evaluation approach.

This section outlines what information is required to conduct an economic evaluation, provides guidance on the most appropriate methods of analysis, and identifies issues that may be encountered.

## 2.1. Introduction

Economic evaluations of healthcare interventions are most often conducted to inform funding decisions. In these cases there are seven steps to conducting economic evaluations.[63] These are summarised below. However, there is an additional eighth step that needs to be considered when conducting economic evaluations to inform scheduling decisions – identifying and measuring patient behaviour changes.

1. Formulate the study frame
2. Patient behaviour changes
3. Identify, measure and value the health outcomes
4. Identify, measure and value the resource use
5. Identify which type of analysis will be conducted
6. Summarise the data
7. Understand uncertainty
8. Interpret the results

When conducing an economic evaluation to inform funding decisions there is a target population – individuals who will receive the healthcare intervention under consideration. This is not as clear cut when it comes to scheduling decisions.

Following the down-scheduling of a medicine not all individuals currently treated with the medicine will switch from obtaining the medicine via a prescription to OTC. Some untreated individuals will

subsequently use the OTC medicine, while some may seek the OTC medicine and be referred to a medical practitioner by the pharmacist or self-refer after reading packaging or other product information. Some individuals may also misuse the medicine[i], or use in the presence of other medicines, contraindications or precautions.

On the other hand, following the up-scheduling of a medicine some patients may switch from obtaining the medicine via OTC to a prescription, while others may subsequently use other OTC medicines or stop treatment altogether.

Changes in patient behaviour following changes in the schedule of a medicine will subsequently impact health outcomes and resource use. Consequently, economic evaluation to inform funding decisions need to identify and measure patient behaviour changes.

## 2.2. Formulating the study frame

It is considered best practice for health economic evaluations to clearly state what is:

- the healthcare intervention under consideration;
- the comparator(s);
- the patient population of interest;
- the setting and location; and
- the perspective(s) of the analysis.[13, 17]

The time horizon(s) of the analysis should also be clearly stated. What these are likely to be in the context of re-scheduling decisions are described below.

### 2.2.1. Intervention and comparator

In the context of down-scheduling decisions, the healthcare intervention and comparator is clear: the healthcare intervention is the medicine being down-scheduled to being available OTC (e.g. Schedule 3 of the *Poisons Standard)*; and the comparator is that the medicine remains available via prescription only (e.g. listed under Schedule 4 of the *Poisons Standard*). In contrast, the healthcare intervention and comparator are reversed in the context of up-scheduling decisions: the healthcare intervention is the medicine being up-scheduled to being available via prescription only (e.g. Schedule 4*)*; and the comparator is that the medicine remains available OTC (e.g. Schedule 3*)*.

Note that the term 'medicine' may be limited to a certain form and strength of a single compound (e.g. simvastatin 10 mg tablets), a multi-compound (e.g. combined OCPs), or may be as broad as an entire class (e.g. statins).

[i] This includes intentional overdose (e.g. use of more than the recommended dose for self-harm), intentionally misuse with therapeutic intent (e.g. use of more than the recommended dose due to perceived inadequate efficacy or a belief that OTC medicines are less effective, or using the medicine for an extended period), and accidental ingestion (e.g. non-intentional use of a medicine, usually by a child).

### 2.2.2. Patient population

An underlying assumption of many economic evaluations is that a target population will receive the healthcare intervention under consideration.

In the context of scheduling decisions, the key patient population are those with the medical condition(s) currently treated with the proposed medicine to be up or down-scheduled. Alternatively, it may be people for whom preventative treatment with the proposed medicine is recommended (e.g. women using the OCP to prevent pregnancy). However, economic evaluations of scheduling decisions need to include a broader definition of the patient population than typically considered.

For example, other patients with the medical condition (or risk factor) but not currently treated with the proposed prescription medicine to be down-scheduled[ii] may also switch to using the medicine following down-scheduling – these patients should also be included in the economic evaluation. The removal of the need to obtain a prescription from a GP also enables patients who are undiagnosed or who have a different medical condition to that indicated to access the medicine if down-scheduled.

On the other hand, undiagnosed patients or patients with different medical condition(s) currently treated with the proposed OTC medicine to be up-scheduled will be unable to access the medicine following up-scheduling – these patients should also be included in the economic evaluation. These patients may subsequently use other OTC medicines or stop treatment altogether.

Table 2-1 and Table 2-2 show how the patient population can be split into groups based on the presence of the key medical condition(s) that the medicine is licensed to treat, whether the patient is diagnosed and current treatment. Patients who are undiagnosed or have a different medical condition should be unable to access prescription medicines, assuming that medical practitioners are skilled at diagnosis and do not prescribe medicines off-label. Note that some patients may be currently using both prescription only medicines and OTC medicines.

**Table 2-1: Patient groups to be considered for economic evaluations of down-scheduling decisions**

| Current treatment | Patients with the medical condition(s) | | Patients with a different medical condition(s) |
|---|---|---|---|
| | Diagnosed | Undiagnosed | |
| Untreated | Group 1 | Group 6 | Group 9 |
| Non-pharmacological treatment | Group 2 | Group 7 | Group 10 |
| Proposed Rx medicine to be down-scheduled | Group 3 | - | - |
| Another Rx-only medicine | Group 4 | - | - |
| Another OTC medicine | Group 5 | Group 8 | Group 11 |

OTC: over-the-counter; Rx: prescription

[ii] Currently using another prescription only medicine, an OTC medicine, a non-pharmacological treatment or are untreated.

**Table 2-2: Patient groups to be considered for economic evaluations of up-scheduling decisions**

| Current treatment | Patients with the medical condition(s) | | Patients with a different medical condition(s) |
|---|---|---|---|
| | Diagnosed | Undiagnosed | |
| Untreated | Group 1 | Group 6 | Group 10 |
| Non-pharmacological treatment | Group 2 | Group 7 | Group 11 |
| Proposed OTC medicine to be up-scheduled | Group 3 | Group 8 | Group 12 |
| Another Rx-only medicine | Group 4 | - | - |
| Another OTC medicine | Group 5 | Group 9 | Group 13 |

OTC: over-the-counter; Rx: prescription

### 2.2.3. Setting and location

An economic evaluation provides evidence for a decision relevant to a certain place and setting. This includes the country and the particular setting of healthcare (i.e., primary, secondary, tertiary care, or community/public health interventions), as well as any other relevant sectors (e.g. education or legal system).[17]

It is likely that proposed prescription medicines to be down-scheduled have been available via prescription for a number of years, and are commonly prescribed by GPs. In contrast, newer medicines are more likely to be prescribed by specialists. GPs are also likely to be comfortable with prescribing the proposed OTC medicines to be up-scheduled. Therefore the relevant healthcare setting will be the primary healthcare system.

### 2.2.4. Perspective

The perspective is the viewpoint from which the resource use is evaluated – thus it determines which costs are included and excluded. There are several perspectives that an economic evaluation can take, including: a patient's perspective, a healthcare provider's perspective (e.g. hospital), a healthcare payer's perspective (e.g. Government), a healthcare system perspective, or a societal perspective.[17] Table 2-3 provides an example of the resources, and thus costs, included under each perspective.

**Table 2-3: Resources included in economic evaluations, by perspective**

| Resource | Patient | Healthcare provider (e.g. hospital) | Healthcare payer (e.g. Government) | Healthcare system | Societal |
|---|---|---|---|---|---|
| Hospitalisations | ✗ | ✓ | ✓ | ✓ | ✓ |
| GP time | ✗ | ✗ | ✓ | ✓ | ✓ |
| GP co-payments | ✓ | ✗ | ✗ | ✓ | ✓ |
| OTC medicines (not listed on PBS) | ✓ | ✗ | ✗ | ✓ | ✓ |
| Prescription medicines (listed on PBS) | ✗ | ✗ | ✓ | ✓ | ✓ |
| Travel | ✓ | ✗ | ✗ | ✗ | ✓ |
| Patient's time off work | ✓ | ✗ | ✗ | ✗ | ✓ |

OTC: over-the-counter; Rx: prescription

In Australia, the guidelines used by the PBAC stipulate that economic evaluations should be taken from a healthcare system perspective.[iii](19) The healthcare system perspective includes direct medical care costs regardless of who incurs them – thus it includes costs incurred by the patient, and public and private healthcare providers (including private health insurance, and other organisations, such as workers compensation). On the other hand, the healthcare system perspective does not include costs associated with travel or patient's time off work.

In order to maintain consistency in decision making across committees of the Australian Government Department of Health and its Agencies (including the TGA), economic evaluations for considering scheduling decisions could take a similar approach to submissions for listing a medicine on the PBS, whereby the primary economic evaluation is taken from a healthcare system perspective. The Office of Best Practice Regulation does not suggest a perspective, however states that "the costs and benefits to all people residing in Australia" should be considered".(22) An economic evaluation may report results from more than one perspective.

If decision makers are also interested in productivity costs, the results of the economic evaluation including productivity costs should be presented as a supplementary analysis, as per the PBAC guidelines. This is due to the risk of double-counting productivity costs with utility values, and due to equity implications.(19)

### 2.2.5. Time horizon

The time horizon refers to the length of time over which costs and consequences are being evaluated. The time horizon should be long enough to capture all relevant costs and consequences(13, 16, 19, 22), and so is highly dependent on the condition that the medicine aims to treat or prevent (e.g. acute versus chronic, once-off versus reoccurring), the duration of efficacy and the duration of adverse events.

In the context of scheduling decisions, the most appropriate time horizon will most likely be the lifetime of the patient. However, it may be shorter if the treatment is for an acute condition (e.g. fungal infections) and there are no long-term impacts of treatment on the disease or long-term adverse events (e.g. strokes). An economic evaluation may report results for more than one time horizon.

## 2.3. Estimating behaviour change

The scheduling of a medicine affects patients' access to medicines. Thus scheduling decisions can result in different patterns of use of different medicines, treatment rates, and adherence rates. Consequently, it is necessary to estimate the proportion of patients in each patient-group before and after the scheduling change.

RCTs are considered the 'gold standard' approach to measuring the impact of a health intervention because the randomisation process reduces the potential for bias due to observed and unobserved factors (e.g. selection bias).(64, 65) However, it is not possible to conduct RCTs of scheduling decisions as they are a nation-wide policy decisions. Consequently estimating the impact on patient behaviour will rely on other approaches.

[iii] Alternative perspectives can be presented as supplementary information or a sensitivity analysis.

### 2.3.1. Before re-scheduling

An epidemiological approach to measuring the proportion of patients in each patient group before the scheduling change will be required, as using a market share approach alone will not capture patients who are not currently treated.

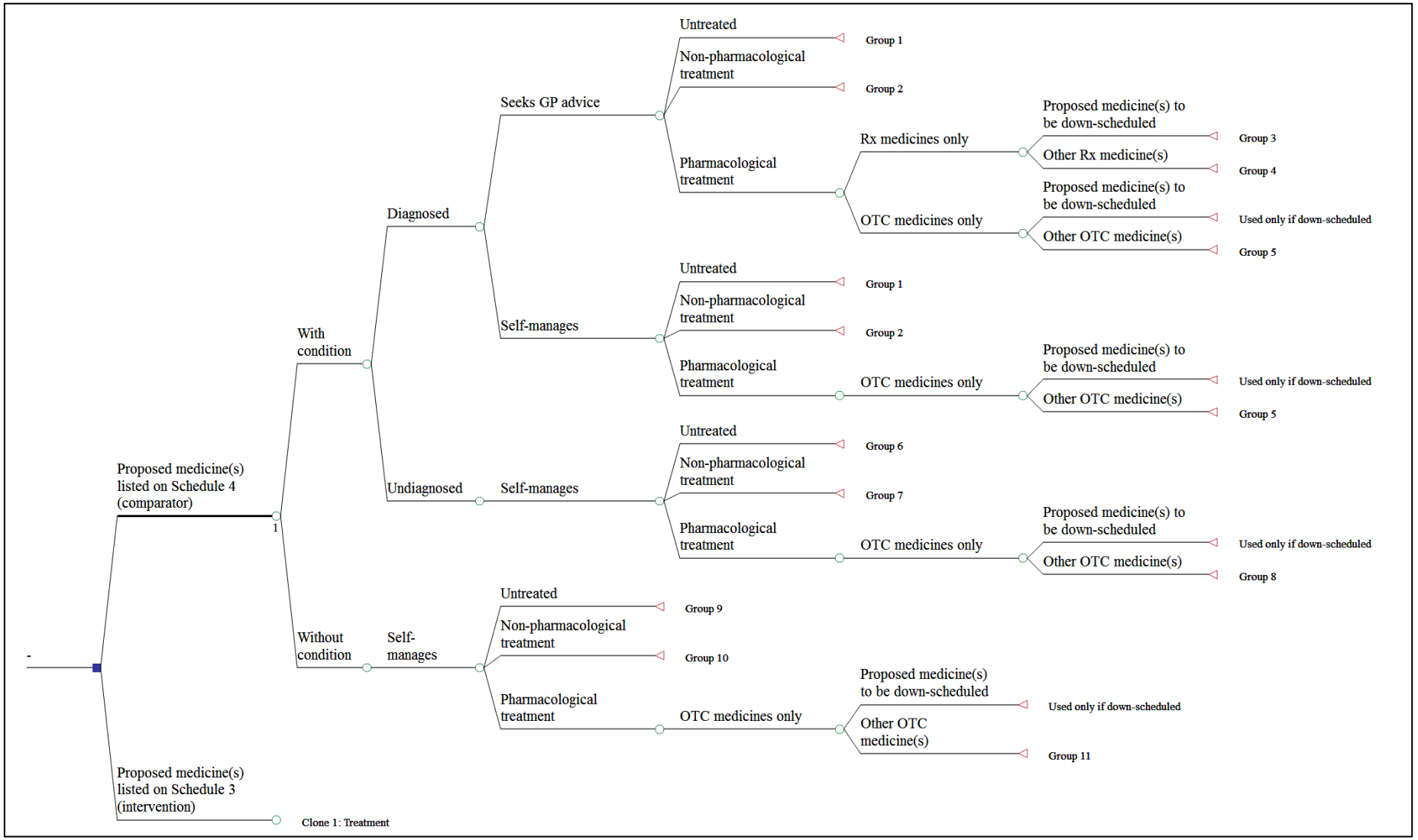
In order to identify the different parameters required, a treatment algorithm should be developed. Generalised treatment algorithms are provided in Figure 2-1 and Figure 2-2, which is mapped to the patient groups identified in Table 2-1 or Table 2-2.

#### *2.3.1.1. Data sources*

It is unlikely a single data source will provide all the information required to populate an economic model and a range of data sources will inform each parameter. A list of potential data that may inform each parameter is provided in Table 2-4. Examples of pre-existing Australian data that may be used are also listed.

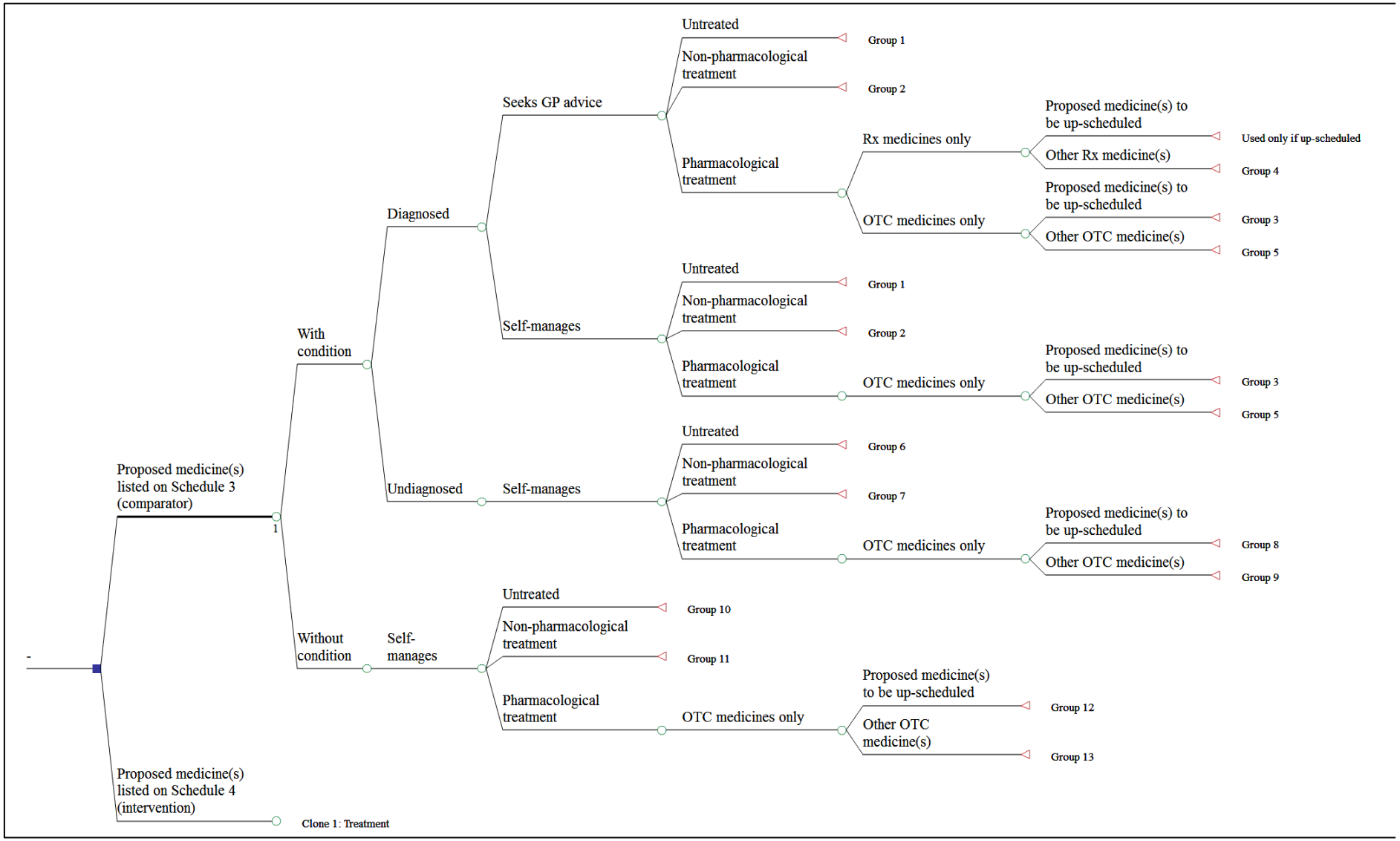
For all parameters, a previously published study may also report the data required and so a systematic literature review should be considered. The data source used for each parameter and methods of analysis should be clearly stated. The best available data should be used where possible, and any limitations or the potential for bias, and the directions of that bias, should be identified. Where multiple sources of data are available to estimate a parameter, sensitivity analysis should be conducted using the different data sources (see Section 2.7.2).

**Figure 2-1: Generalised treatment algorithm for down-scheduling**




GP: general practitioner; OTC: over-the-counter; Rx: prescription.

**Figure 2-2: Generalised treatment algorithm for up-scheduling**




GP: general practitioner; OTC: over-the-counter; Rx: prescription.

**Table 2-4: Potential data sources**

| Parameter | Data sources | Examples of pre-existing Australian data |
|---|---|---|
| Prevalence or incidence of the medical condition | • Case registries<br>• Mortality registers<br>• Large, prospective, observational cohort studies with diagnosis of the medical condition by a medical practitioner | • National Notifiable Diseases Surveillance System<br>• Cancer registries |
| | • Large patient-reported surveys | • ABS National Health Survey<br>• ALSWH, TtM, HILDA, and the 45 and Up Study |
| Probability patient seeks advice from a medical practitioner vs. self-manage | • Patient surveys (e.g. if asked questions about whether they saw a GP about their medical condition) | • As above |
| Probability patient is treated, given they sought advice from a medical practitioner | • Medical practitioner surveys (e.g. if asked questions about, for each patient treated or on average, what treatments they recommended or prescribed) | • BEACH |
| | • Medical records | • NPS MedicineInsight and Medical Director |
| | • Patient surveys (e.g. if asked questions about current treatments, or linked to health administrative data) | • ALSWH, TtM, HILDA, and the 45 and Up Study |
| Probability patient is treated, given they self-manage | • Patient surveys (e.g. if asked questions about current treatments) | • As above |
| | • Pharmacy sales data<br>• Grocery sales data | • IMS Health data<br>• AC Nielsen data |
| The market share of each treatment used | Subsidised prescription medicines:<br>• Health administrative data<br>• Patient surveys (e.g. if asked questions about current treatments, or linked to health administrative data)<br>• Medical practitioner surveys (e.g. if asked questions about, for each patient treated or on average, what treatments they recommended or prescribed)<br>• Medical records | • 10% PBS sample, linked 10% PBS-MBS sample<br>• ALSWH, TtM, and the 45 and Up Study<br>• BEACH<br>• NPS MedicineInsight and Medical Director |

| Parameter | Data sources | Examples of pre-existing Australian data |
|---|---|---|
| | Non-subsidised medicines and OTC medicines:<br>• Patient surveys (e.g. if asked questions about current treatments, or linked to health administrative data)<br>• Medical practitioner surveys (e.g. if asked questions about, for each patient treated or on average, what treatments they recommended or prescribed)<br>• Medical records<br>• Pharmacy sales data | • ALSWH, TtM, and the 45 and Up Study<br>• BEACH<br>• NPS MedicineInsight and Medical Director<br>• IMS Health data |
| Adherence to treatment | • Longitudinal patient surveys (e.g. if asked questions about current treatments, or linked to health administrative data)<br>• Health administrative data<br>• Medical records | • ALSWH, TtM, and the 45 and Up Study<br>• 10% PBS sample, linked 10% PBS-MBS sample<br>• NPS MedicineInsight and Medical Director |
| Concession card status | • PBS-listed prescription medicines that cost over the co-payment<br>• Patient surveys (e.g. if asked about concession card status) | • Australian Statistics on Medicines<br>• ALSWH, TtM, and the 45 and Up Study |

ABS: Australian Bureau of Statistics; ALSWH: Australian Longitudinal Study on Women's Health; BEACH: Bettering the Evaluation and Care of Health; HILDA: Household, Income and Labour Dynamics in Australia; OTC: over-the-counter; PBS: Pharmaceutical Benefits Scheme; NPS: National Prescribing Service; TtM: Ten to Men: The Australian Longitudinal Study on Male Health.

#### 2.3.1.2. Expert elicitation

When data are not available, parameter values may be elicited from experts. Reporting guidelines regarding how expert opinion should be elicited are available.[66] However, expert opinion is considered to be one of the least reliable sources of evidence.[67]

In order to elicit parameter values from experts, several issues must be considered.[68] The first issue to consider is the selection of experts – who and how many. In the case of scheduling decisions, the most likely experts will be GPs, as they would be best placed to estimate how a condition is currently treated in the primary healthcare setting. Caution should be exercised when selecting experts to avoid the overrepresentation of a certain opinion or behaviour, which will bias the results.[69] Conflicts of interest should be identified and minimised. Grigore et al (2013) conducted a systematic review of expert elicitation in economic evaluations and found that the median and mean number of experts was 5.0 and 9.2 (range: 3 to 23 experts), respectively.[69]

The second issue to consider is how parameter values will be elicited – whether training of experts in probabilities and probability distributions is required, how the questions are framed, whether the opinions are elicited face-to-face or self-administered, and the elicitation method. Caution should be exercised when posing questions as it may unintentionally influence the results.[70]

Whether the opinions are elicited face-to-face or self-administered largely depends on the number of experts, whether a group or individual approach is taken, and whether it is possible to coordinate experts. Grigore et al (2013) reported that the most common approach used in economic evaluations is the self-administered approach.[69] A range of elicitation methods are used in economic evaluations, however Grigore et al (2013) reported that the most common elicitation methods used are[69]:

- The histogram technique: The expert is presented with a frequency chart (or histogram) where they are asked to place a number of crosses (or chips or tokens) representing the probability of a certain value. Placing all the crosses in one column represents complete certainty, while placing the crosses equally across all the columns represents complete uncertainty.[68, 69]
- The bisection method: The expert is asked a series of questions to elicit the median and the lower and upper quartiles (or lower and upper 95% confidence intervals). For example, the median is elicited by asking experts the value X where the 'true value' is equally likely to be less than or greater than X.[69]

The third issue to consider is whether the results will be aggregated using a behavioural approach or a mathematical approach. A Delphi panel is an example of a behavioural approach to aggregating the results. First, each expert provides their estimate with some explanation as to their view. This is then supplied to all the other experts in the group (anonymously). The experts can then revise their estimates given the views of the other experts. This process is repeated until the experts' estimates converge.[68] This approach assumes that a consensus can be reached.

However, when estimating parameters such as medical practitioner prescribing behaviour, not all medical practitioners may think or act the same way. A mathematical approach generally involves fitting some parametric distribution to the individual estimates and then across the estimates. A detail overview of these approaches is described by O'Hagan et al (2006).[68] A behavioural approach to aggregating results may be reasonable when attempting to estimate mean parameter values, however a mathematical approach is more likely to be suitable as the uncertainty around the mean parameter value in terms of a probability distribution can also be estimated.

#### 2.3.1.3. Assumptions

Assumptions are regularly made in economic evaluations when there is a lack of data and no opportunity to survey patients and medical practitioners. However, assumptions are subject to high levels of uncertainty.

Any assumptions should be clearly stated and extensive sensitivity analysis should be conducted (see Section 2.7). A conservative approach should be considered, where the chosen value favours the comparator. This approach will bias the results towards finding that down-scheduling or up-scheduling is not cost-effective, however it will also increase the robustness of the decision when the base case estimates suggest that down-scheduling or up-scheduling is cost-effective.

In the case of scheduling decisions, it is often reasonable to make some simplifying assumptions. For example, it may be reasonable to assume that all patients choose some form of treatment if the symptoms of the disease are severe. Similarly, it may be reasonable to assume that all patients have the medical condition if the medicine proposed to be down-scheduled or up-scheduled has limited applications (e.g. anti-fungal treatments), or it may be reasonable to assume that all patients are treated with a prescription medicine if there are no other OTC medicines or no non-pharmacological treatments available to treat the condition.

### 2.3.2. After re-scheduling

Six approaches may be used to predict the proportion of patients in each patient group after down-scheduling or up-scheduling. These approaches are summarised in Table 2-5 and the methods, strengths and limitations of each approach are detailed below.

Different approaches may be used to estimate the impact of scheduling decisions on different parameters. For example, predictions of the impact of down-scheduling on patients choosing to self-manage and then choosing an OTC medicine compared to no treatment could be based on stated preference survey. Similarly, predictions of the change in choice of medicine could be based on observational prescription and OTC sales data from overseas markets. Different approaches could be applied as a sensitivity analyses to test the robustness of the results.

**Table 2-5: Approaches to estimating behaviour change after down-scheduling**

| Approach | Strengths | Weaknesses |
|---|---|---|
| Observational data regarding usage of a similar medicine | • Revealed preferences<br>• Accounts for adherence<br>• Health-system specific | • Dependent upon a similar medicine being previously down-scheduled or up-scheduled<br>• Assumes no difference in the attributes of the medicines<br>• Ignores first-mover advantage |
| Observational data from overseas markets | • Revealed preferences<br>• Accounts for adherence<br>• Accounts for lags in switching<br>• Similar attributes of the medicines | • Dependent upon the medicine being down-scheduled or up-scheduled overseas<br>• Assumes no difference in health systems or patient preferences across countries |

| Approach | | Strengths | Weaknesses |
|---|---|---|---|
| Stated preference surveys | General surveys | • Applicable if first time the medicine is down-scheduled or up-scheduled<br>• Health-system specific<br>• Can account for differences in the attributes of the medicines<br>• Can estimate impact of changes in subsidisation status<br>• Can estimate switch behaviour for different types of patients (e.g. concession card holders)<br>• Can estimate the proportion of patients who choose no treatment or continue to seek advice from a medical practitioner | • Hypothetical preferences<br>• Risk of bias through vignette and the questions posed<br>• Assumes patients and medical practitioners switch choice instantly<br>• Assumes perfect adherence |
| | Discrete choice experiments | • Applicable if first time the medicine, or a similar medicine, is down-scheduled or up-scheduled<br>• Health-system specific<br>• Can account for differences in the attributes of the medicines<br>• Can estimate impact of changes in subsidisation status<br>• Easy to understand<br>• Evidence of external validity<br>• Can estimate the proportion of patients who choose no treatment or continue to seek advice from a medical practitioner | • Hypothetical preferences<br>• Assumes that patients and medical practitioners are aware of all possible treatment options in real-life<br>• Assumes that attribute levels used to predict usage are reflective of opinions of patients and medical practitioners in real-life.<br>• Assumes patients and medical practitioners switch choices instantly<br>• Assumes perfect adherence |
| Expert elicitation | | • Applicable if first time the medicine, or a similar medicine, is down-scheduled or up-scheduled<br>• Applicable if there is no opportunity to survey patients and limited opportunity to survey medical practitioners | • Hypothetical preferences<br>• Dependent upon selection of experts, how expert opinion is elicited and aggregated<br>• Highly uncertain |
| Assumptions | | • Applicable if first time the medicine, or a similar medicine, is down-scheduled or up-scheduled<br>• Applicable if there is no opportunity to survey patients and medical practitioners | • Highly uncertain |

#### 2.3.2.1. Observational data regarding usage of a similar medicine

Observational, longitudinal data on the usage of a similar medicine before and after changing schedules in the same country may be used to predict patient switching between prescription and OTC. For example, usage of omeprazole 10 mg following down-scheduling could be used to predict the impact of down-scheduling pantoprazole 20 mg.

Potential data sources are listed in Table 2-4. Observational data on the usage of other related prescription medicines and OTC medicines that may also be affected by changing scheduling should also be analysed to identify whether there is any switching between these medicines.

There are several issues to consider when analysing this type of data, which can be addressed using econometric analysis.

- A difference-in-difference approach should be applied to avoid overestimating (underestimating) the impact of down-scheduling on usage if the usage of a medicine is increasing (decreasing) over time prior to down-scheduling (and vice versa for up-scheduling). This approach involves analysing longitudinal data on the usage of the therapeutically equivalent medicine, and other related prescription and OTC medicines, using either unrelated medicines or the same medicines but in another country as a control.
- Seasonal dummies should be applied if usage has a seasonal component. For example, influenza is more prevalent over winter months. Moreover, in Australia, patients may stock up on PBS medicines in the last two months of the year due to the safety net rules.(71)
- In the case of down-scheduling, a wash-out period (e.g. three months) should be applied as switching is unlikely to be instantaneous, particularly given many patients will have prescription repeats or if the medicine is not advertised. This is not necessary in the case of up-scheduling.
- Interaction terms may be applied to estimate differences in switching behaviour by sub-groups if patient-level data are available (e.g. concession card holders).

The key strength of using observational data on the use of a similar medicine in the same country is that true medical practitioner and patient preferences are revealed by their switching behaviour.[iv] It also accounts for differences in adherence if medicines are used on an ongoing basis. Finally, there is no need to account for differences in healthcare systems.

Conversely, the approach is highly dependent on a similar medicine changing schedules previously (i.e. not first-in-class to be down-scheduled/up-scheduled). It also assumes there are no differences in the attributes of the medicine that may impact relative demand, such as efficacy, mode of administration, price and the adverse event profile. The impact of these attributes could be taken into account by applying additional explanatory variables in the econometric analysis. Although in practice this may be hindered by the number of medicines that have changed schedules and a lack of variability across some attributes (e.g. patient co-payments and mode of administration). The latter limits the ability to measure how much weight is placed on each attribute and thus whether differences in the attributes of the medicines drive demand or would be largely ignored compared to other attributes.

There also exists persistence in decision making as medical practitioners and patients are often risk averse or reluctant to change their habits, and unwilling to switch treatments if the current treatment is reasonably effective and tolerated.(72) Consequently, the observed change in usage following re-scheduling the first medicine is unlikely to be observed to the same extent following re-scheduling similar medicines. This is referred to as ‘first-mover advantage’.

#### *2.3.2.2. Observational data from overseas markets*

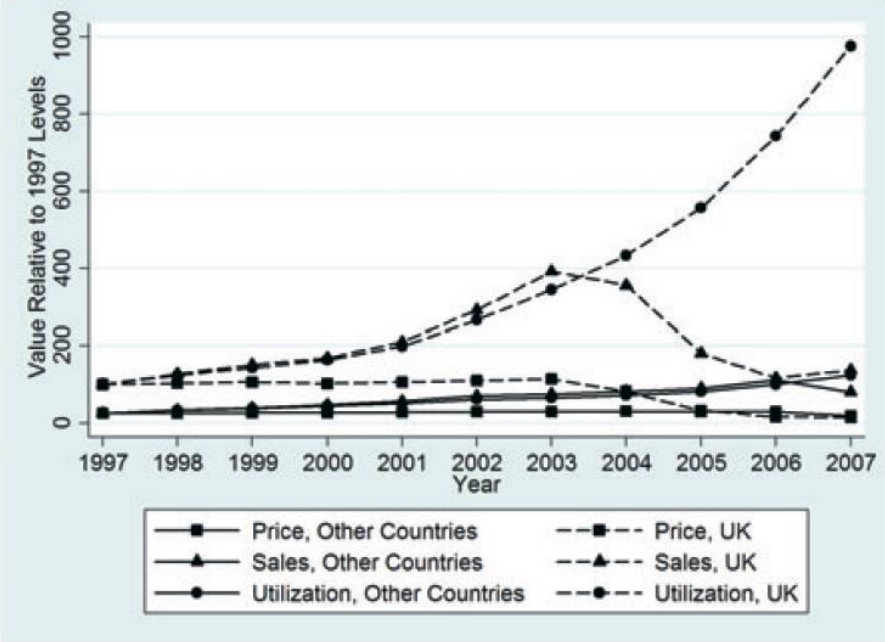
Observational data on the usage of the same medicine before and after changing schedules in overseas markets can be used to predict patient switching between prescription and OTC use. The data should be analysed using a similar approach to that described above. For example, usage of simvastatin following down-scheduling in the UK could be used to predict the impact of down-scheduling simvastatin in Australia. Box 2-1 presents an example of an analysis of observational data from overseas markets.

[iv] Not applicable usage of the drug in another country is used as a control.

### Box 2-1: Difference-in-differences analysis of observational data

Sood, Sun and Zhuo (2012) used a difference-in-differences approach to estimate how the down-scheduling of simvastatin 10 mg in the UK affected utilisation, prices and expenditures.[73] The analysis used panel data from IMS Health on prescriptions and OTC sales of simvastatin between 1997 and 2007 from the UK. Similar data from four other countries were used as the controls. The analysis also controlled for patent expiration and the introduction of generics. The analysis found that down-scheduling simvastatin increased overall utilisation by 64%. Unfortunately, the impact on prescription versus OTC simvastatin was not reported, nor was the impact on other statins.

**Simvastatin utilisation, prices and expenditures, 1997-2007**




Source: [73]

The strengths of this approach is that true medical practitioner and patient preferences are revealed by their switching behaviour, it accounts for adherence and any lags in switching, and the medicines are more likely to have similar attributes.

Conversely, the approach is dependent upon the medicine changing schedules somewhere overseas and assumes that the healthcare systems are similar. In particular, the approach assumes there is similarity in the cost of medicines, the out-of-pocket cost of a GP consultation, pack sizes, advertising, and the existence of a Pharmacist Only (Schedule 3) medicine category. In some countries there may also be prescribing incentives, such as in the US additional payments to medical practitioners are made for intramuscular injection of medicines[v] but in other countries these payments are not made (such as in Australia[vi]).[74] Finally, the impact of re-scheduling a vaccine may vary between countries because of differences in: the risk of infection; funding; uptake by other individuals, thus conferring herd immunity; the strength of anti-vaccination sentiment; preferences for risk-taking behaviour; and incentives to vaccinate (such as school-entry requirements).

[v] CPT/HCPCS (Level II) codes 96401 and 96402 in the US
[vi] Medicare Benefits Schedule - Note G11.1

#### 2.3.2.3. Stated preference survey

A stated preference survey involves surveying individuals about their change in behaviour following down-scheduling or up-scheduling a medicine. Box 2-2 presents an example of a stated preference survey administered to patients to assess the down-scheduling of the OCP.

As some patients may continue to seek advice from a medical practitioner following the down-scheduling of a medicine, questions should be included regarding whether they obtained advice from a GP and their current treatment (including no treatment, and non-pharmacological treatments), and whether they will continue to obtain advice from a GP. Medical practitioners could also be surveyed regarding what medicines they would prescribe, or which medicines they would recommend the patients obtain OTC, following re-scheduling a medicine (see Section 2.3.1.2).

**Box 2-2: Stated preference survey**

Foster et al (2015) used a stated preference survey of 2046 women in November-December 2011 to estimate the impact of down-scheduling OCPs.[75] Women were given the following description:

> *"Birth control pills would be available on a shelf at a drug store or grocery store just like cough medicine or some allergy pills. If you had a question, you could talk to a pharmacist. You would not need a prescription from a doctor or nurse. If you have insurance, your insurance may or may not cover 'OTC' birth control pills."*

Women reported whether they were "very likely", "somewhat likely" or "not likely" to use OCPs if they were available OTC, or "not sure" or "not interested in birth control pills" regardless of OTC access. The rate of switching was predicted based on: a) assuming that 100% of those patients who reported that they were "very likely" to switch would switch in practice, b) assuming that 100% of those patients who reported that they were "very likely" or "somewhat likely" to switch would switch in practice. The rate of switching was calculated by current contraceptive method used. Women were also asked the highest amount they were willing and able to pay for a one-month supply of OCPs if available without a prescription. This data were used in a sensitivity analysis of the impact of out-of-pocket costs on the rate of switching.

**Likelihood of using OTC oral contraceptives among low-income women, by method women report currently using**

| | Very likely (n=177) | Somewhat likely (n=126) | Not likely (n=576) | Total (n=879) |
|---|---|---|---|---|
| IUD | 16% | 8% | 76% | 100% |
| Implant | 0% | 11% | 89% | 100% |
| Shot (injection) | 2% | 14% | 84% | 100% |
| Pill | 36% | 20% | 45% | 100% |
| Ring | 0% | 0% | 100% | 100% |
| Patch | 0% | 0% | 100% | 100% |
| Condom | 21% | 26% | 53% | 100% |
| Withdrawal | 30% | 0% | 70% | 100% |
| Rhythm | 20% | 27% | 53% | 100% |
| None | 15% | 10% | 74% | 100% |
| Total | 21% | 15% | 65% | 100% |

Source: [75]

The strengths of this approach is that it can be applied if it is the first time the schedule is changed for a medicine, or a similar medicine. The survey can also be healthcare system specific and take into account differences in the attributes of the medicines that may impact relative demand through the use of the vignette. Asking patients how much they are willing to pay if the medicine is down-scheduled allows sensitivity analysis to be conducted on the removal of any subsidies (e.g. delisted from the PBS schedule). The results can also be analysed by sub-groups (e.g. concession card holders). Finally, the approach can also be used to estimate the proportion of patients who continue to seek advice from a medical practitioner, choose a non-pharmacological treatment or choose no treatment at all.

The key limitation of the approach is that the survey is hypothetical and there may be some discrepancy between the patient's hypothetical choice and their actual choice.[76-78] In particular, the results may be biased when patients are asked about their willingness to pay. The results are also highly dependent on the vignette and the questions posed. Particular care should be taken to avoid any potential framing bias and thus encourage respondents to choose a particular response. Furthermore, the approach assumes that the respondent is fully informed about the treatments, or that any differences between the treatments do not affect patient choices if any relevant information is excluded (e.g. efficacy or adverse events). The results may also be affected by the exclusion of a treatment strategy outside of the presented options if in reality some patients are likely to choose this treatment option (e.g. "no treatment" or "non-pharmacological treatment"). The approach assumes perfect adherence in the long-term – usage may be lower than that experienced in the real-world. Further analysis or assumptions may be required (see Section 2.3.3.2).

Finally, the approach assumes that patients and medical practitioners switch instantly. In the case of down-scheduling this is optimistic given there is persistence in decision making; in that medical practitioners and patients are often risk averse and unwilling to switch treatments if the current treatment is reasonably effective and tolerated.[72] When applying the results in an economic model, especially a Markov model, an adoption curve may be applied reflecting that switching will not be instant. The shape of the curve can be informed by the speed of switching of a previously down-scheduled medicine. In the case of up-scheduling, this assumption may be considered reasonable.

#### 2.3.2.4. Discrete choice experiments

Discrete choice experiments can be used to estimate the demand for healthcare, and thus can be used to predict the impact of scheduling changes.[79-81] The underlying theory of a discrete choice experiment is that an individual derives utility from the underlying attributes of a good and preferences (and thus utility) across goods are revealed through their consumption choices.[82] Regarding medicine choice, outcomes such as convenience (e.g. whether available OTC), efficacy, adverse events, and costs could be seen as the underlying attributes from which the individual derives utility.

In a discrete choice experiment respondents are presented with a series of realistic but hypothetical choice sets with each alternative described by a bundle of these attributes, each with a different level.[83] Respondents are then asked to rank the alternatives or choose their most preferred option. The strength of this approach is that choosing between bundles of goods is an easily comprehended task for respondents.

Reporting guidelines regarding how discrete choice experiments are designed are available and should be followed, including the use of focus groups or patient surveys to identify the attributes, the selection of choice sets, the questions posed, and whether the discrete choice experiment is piloted.[84]

The data from discrete choice experiments are analysed using several econometric models, with various underlying assumptions regarding taste and scale heterogeneity. The conditional logit model assumes that for any two alternatives the ratio of the probabilities does not depend on any other alternatives.[85]

In other words, when the attribute of an alternative changes such that its market share falls (or the alternative is withdrawn from the market), then the lost market share is gained proportionally by the remaining alternatives such that the ratios are unchanged.(86) When there are three or more options (e.g. different medicines), it is hard to see this assumption being reflective of reality with regards to preferences across medicines where there is likely to be close substitutes (i.e. same compound, different modes of administration). Consequently other models should be considered when there are three or more options, such as the nested logit, multinomial probit or mixed probit, which allow for differential substitution patterns.(86)

In order to predict the proportion of patients switching treatment following re-scheduling a medicine, first the attribute levels for each available treatment option is selected, and second these attribute levels are combined with the coefficient estimates from the discrete choice experiment. How these two sets of data are combined is dependent upon how the discrete choice experiment was analysed. For example, the following equation is used to estimate the probability ($\pi$) of patient $i$ choosing treatment option 1 of J options, where the data were analysed using a conditional logit model, $x$ represents the attribute levels for each treatment option and $\beta$ represents the coefficients:

$$\pi_{i1} = \frac{e^{x_{i1}\beta}}{\sum_{j=1\ to\ J} e^{x_{ij}\beta}} \qquad \text{Equation 1}$$

While conditional logit and nested logit models have a closed form solution, other models do not. Thus the choice probabilities need to be simulated to approximate the integration of choice situations/respondents.(87) It may also be necessary to recalibrate the results based on the observed proportion of patients choosing each treatment option before the change in schedule through the use of alternative-specific constants.(86)

Box 2-3 presents an example of a discrete choice experiment administered to patients estimating the relative importance of various factors that influence whether patients prefer to manage symptoms themselves versus seeking healthcare. Although in practice, a discrete choice experiment used to predict the impact of re-scheduling a medicine should be more context specific and include attributes such as efficacy and the risk of adverse events, in addition to whether the medicine is available via prescription only or OTC, time to treatment and cost. Note that the inclusion of a cost variable can be used to estimate the impact of changes in subsidisation status following down-scheduling.

Scenario analysis can be conducted to estimate the impact of advertising, by randomising patients to a group that views an advertisement and one that does not view an advertisement before completing the discrete choice experiment.(60)

It may also be worth administering the discrete choice experiment to medical practitioners to explore changes in their recommendations if a medicine is available OTC compared to prescription only as some patients may continue to seek advice from a medical practitioner.

**Box 2-3: Discrete choice experiment**

Rennie et al (2010) conducted a discrete choice experiment in the UK (N=480) in order to estimate the relative importance of various factors that influence whether patients prefer to manage symptoms themselves versus seek healthcare.(88) Three case studies were considered: rectal bleeding, back pain and diarrhoea symptoms. The attributes considered included: the type of healthcare received (GP, Practice Nurse, Pharmacy, Complementary, NHS24/NHS Direct, Self-care, Do nothing), availability of healthcare (in hours or days), and cost to the patient (in Great British Pounds, GBP). An example question is provided below:

**Which option would you choose?**

| | Option 1 | Option 2 |
|---|---|---|
| Type of management | Self-care | GP |
| Availability | 0 hours | 5 days |
| Cost | £20 | £10 |

(Tick one box only)

☐ Option 1

☐ Option 2

☐ Do nothing

The data were analysed using a conditional logit model. A table of the results is provided below:

| Variable | Coefficient (95%CI) | | |
|---|---|---|---|
| | Diarrhoea | Back pain | Rectal bleeding |
| Constant | 1.31 (1.12, 1.50) | 1.22 (1.03, 1.42) | 0.91 (0.68, 1.14) |
| Management type | | | |
| Pharmacy | -0.15 (-0.31, 0.01) | 0.06 (-0.11, 0.23) | 0.73 (0.56, 0.90) |
| GP | -0.50 (-0.71, -0.28) | 0.69 (0.48, 0.90) | 1.98 (1.74, 2.23) |
| Practice nurse | -0.61 (-0.80, -0.41) | 0.22 (0.03, 0.41) | 1.34 (1.15, 1.53) |
| Complementary | -1.12 (-1.34, -0.90) | -0.35 (-0.55, -0.14) | -0.17 (-0.37, 0.04) |
| NHS24/NHS Direct | -0.56 (-0.74, -0.39) | -0.06 (-0.24, 0.11) | 1.00 (0.82, 1.18) |
| Availability (days) | -0.18 (-0.23, -0.14) | -0.13 (-0.17, -0.09) | -0.16 (-0.20, -0.11) |
| Cost (£) | -0.061 (-0.067, -0.054) | -0.055 (-0.061, -0.049) | -0.040 (-0.045, -0.034) |
| Log-likelihood | -4118.3873 | -4160.5094 | -3648.2565 |
| Number of individuals (observations) | 473 (12,771) | 473 (12,771) | 473 (12,771) |

The results indicated that patients preferred to seek care from a pharmacy compared to a GP for diarrhoea, but preferred to see a GP for rectal bleeding and back pain. Patients were willing to pay £4, £2.34, and £2.77 to reduce waiting time for rectal bleeding, back pain, and diarrhoea respectively.

Using Equation 1 and assuming that it takes one hour to see a pharmacist, two days to see a GP, and the medicine costs £10 if they obtained the medicine OTC compared to £3.16 if they received a prescription, then the probability of seeking care from a pharmacy for back pain would be 32%. However, if the medicine also costs £3.16 if they obtained it OTC, then the probability of seeking care from a pharmacy would increase to 41%.

Source: [88]

Similar to the stated preference approach, discrete choice experiments can be applied if the schedule of the medicine, or a similar medicine, is to be changed for the first time. They are able to be healthcare system specific and take into account differences in the attributes of the medicines that may impact relative demand. The approach is hypothetical and there may be some discrepancy between the patient's hypothetical choice and their actual choice. However, there is some evidence that discrete choice

experiments are able to predict choices within sample[89-91] and out of sample[80, 92-95], although further research is required.

The limitations of discrete choice experiments relate to several underlying assumptions. First, that respondents are aware of all possible treatment options in real life.[96] This is less likely for patients than for medical practitioners. The predicted usage is unlikely to reflect real life if the respondents are unaware of some treatment options. Consequently calibration of the results may be required so that it predicts current choices.[86] Second, the selected attribute levels used to predict usage are reflective of the opinions of patients and medical practitioners in real-life. This is likely to be a bigger issue for subjective attributes such as efficacy compared to objective attributes, such as whether the medicine is available by prescription only. Again, the approach assumes that patients and medical practitioners switch their choices instantly.[96] To address the above issues patients could be surveyed regarding: their awareness of the treatment options; the attributes that they considered relevant to their decision making; opinions regarding the attribute levels of each treatment option; and whether they would switch. Furthermore, an adoption curve may be applied in the economic model.

Finally, the approach assumes perfect adherence in the long-term,[80] and so the predicted usage may be lower than that experienced in the real-world. Further analysis or assumptions may be required (see Section 2.3.3.2).

#### 2.3.2.5. Expert opinion

See Section 2.3.1.2 for a detailed discussion.

#### 2.3.2.6. Assumptions

See Section 2.3.1.3 for a detailed discussion.

### 2.3.3. Other issues to consider

#### 2.3.3.1. Pharmacist behaviour

Pharmacists play a key role in the treatment of patients. A recent Australian survey found that 63.8% of patients with chronic conditions obtained advice from a pharmacist about treatment, [vii] 30.8% obtained advice about whether a doctor's visit is necessary from a pharmacist, and 23.2% accessed health screening or monitoring services (N=442).[97] In Australia, the Sixth Community Pharmacy agreement provides funding for existing community pharmacy programs (such as MedsCheck and Diabetes MedsCheck), and trials of new pharmacy programs (such as pharmacy based screening and referral for diabetes).[98]

Consequently, pharmacist behaviour will have an impact on the proportion of patients switching from obtaining a medicine via prescription compared to OTC. For example, patients may seek the advice of a pharmacist about treatment options for their condition, rather than (or in addition to) the advice of a medical practitioner. Furthermore, a pharmacist may choose to withhold supply of a Pharmacist Only (Schedule 3) medicine if they consider it inappropriate. Finally, some countries have introduced pharmacist training and require the use of a screening tool (or administer a survey) before supplying some OTC medicines. Such an approach was used when down-scheduling trimethoprim in New Zealand.[26]

The probability that a pharmacist will recommend treatment with a down-scheduled medicine could be estimated by using hypothetical patients, or by using real patients where no medicines are dispensed, and

[vii] Could be an ad hoc discussion or counselling session, or involve a more structured medications review.

surveying pharmacists regarding which patients they would dispense medicines. Box 2-4 presents an example of such a study conducted in Europe.

The probability that a pharmacist will recommend treatment with a down-scheduled medicine could also be estimated by conducting a pilot where medicines are dispensed. For example, OCPs dispensing without a prescription has been piloted in the US and the UK.[99-101] The clinical audit of the UK pilot found that the pharmacists had adhered to the Patient Group Direction, made clinically appropriate supplies and referred correctly in all the cases reviewed.[101] Unfortunately detailed results of the audit on the appropriateness of pharmacist dispensing were not reported.

**Box 2-4: Concordance study**

Symonds et al (2011) conducted a survey of pharmacists and GPs in the UK, Germany, Spain and the Czech Republic (N=53 pharmacists and 13 GPs).[102] Pharmacists were provided education regarding erectile dysfunction and product information about sildenafil 50 mg (including who would not be appropriate for treatment), and additional information about supplying the medicine in the pharmacy setting. Ten fictional case studies illustrating the application of the patient-screening questionnaire were also provided.

Patients then visited a participating pharmacy (N=346) and completed the patient-screening questionnaire. Pharmacists then assessed the suitability of treatment with sildenafil 50 mg. No medicine was dispensed. A GP telephoned the patient to conduct an independent clinical assessment to determine the suitability of treatment with sildenafil 50 mg within seven days of the pharmacist assessment.

Concordance between the pharmacist and GP recommendations was 70% (95%CI: 66%, 74%). The concordance increased to 90% (95%CI: 86%, 94%) when the specialist in sexual medicine resolved cases for which the recommendation between the pharmacist and GP did not agree.

The false-positive rate (incorrectly recommended suitability) was 9% for pharmacists and 14% for GPs, and the false-negative rate (incorrectly recommended unsuitability) was 12% for pharmacists and 34% for GPs. In the cases where the pharmacist incorrectly recommended suitability, 35% were due to the contraindication not being reported to the pharmacist on the questionnaire. The remainder were due to the responses to the questionnaire not supporting the pharmacist recommendation. In the cases where the pharmacist incorrectly recommended suitability, 76% were considered critical, including cardiovascular symptoms with moderate exercise or cardiovascular problems; contraindicated medications; and painful erections.

Source: [102]

Pharmacists may also identify risk-factors and refer a patient to consult a medical practitioner following a patient seeking the advice of a pharmacist in relation to an OTC medicine, or due to pharmacists being required to use a screening tool before supplying some OTC medicines. As a result, patients may be diagnosed with a condition earlier and would receive treatment earlier than otherwise. For example, down-scheduling of sildenafil for erectile dysfunction in New Zealand, in combination with a screening tool, may increase cardiovascular disease detection.[32] The probability that a pharmacist will refer an at-risk patient to see a medical practitioner could be estimated by using hypothetical patients, or by using real patients through a pilot.

#### *2.3.3.2. Improved adherence*

For some medicines, treatment effectiveness may differ by the rate of adherence (proportion of doses taken over a defined period) and persistence (the duration of time from initiation to discontinuation). Medicine costs will also be impacted by the rate of adherence and persistence. Consequently, the rates of

adherence and persistence before and after re-scheduling a medicine will need to be estimated for these medicines.

Adherence before re-scheduling a medicine can be measured using observational data, such as dispensing data, and estimating the possession ratio (e.g. quantity dispensed over a six-month period, taking into account dosage). The possession ratio is a proxy for the patient actually taking the medicine. This data can also be used to measure persistence before re-scheduling a medicine by estimating the treatment duration.

The impact of re-scheduling a medicine can be measured by comparing adherence and persistence rates before and after the change using: observational data regarding usage of a similar medicine; or observational data from overseas markets. Note there can be no improvement in adherence if the possession ratio is at its maximum.

In the event of a lack of data, the conservative assumption is to assume that re-scheduling a medicine will not improve adherence.

# 2.4. Identifying, measuring and valuing the benefits and risks

## 2.4.1. Identifying the benefits and risks

There are a range of benefits and risks from changing the level of access to medicines that may be currently considered by regulatory authorities. See Table 2-6 for some examples of benefits and risks. This table was largely based on the Brass framework, however some additional benefits and risks have also been added.[9] Not all benefits and risks will be relevant to all scheduling decisions. For example, down-scheduling a medicine may not always impact public health or increase the risk of intentional overdose.

The key benefits and risks that should be included can be identified through three approaches:

1. A review of key RCTs involving the medicine proposed to be down-scheduled with the aim of identifying the health outcomes;
2. Expert opinion from medical practitioners or pharmacists; and
3. The opinion of patients who are or have been treated with the medicine proposed to be down-scheduled.

The opinion of medical practitioners or patients can be obtained through one-on-one interviews, focus groups or surveys. Which approach depends on whether they have pre-existing opinions about the benefits and risks, or whether it may be considered useful to listen to the opinions of others before they form their own opinions. It may also be worth considering applying more than one approach. For example, a review of RCTs may help develop identify potential questions for interviews and focus groups. Furthermore, patients may place a greater importance on some benefits and risks compared to medical practitioners.

**Table 2-6: Risks and benefits of re-scheduling medicines**

| Factors | Examples |
|---|---|
| **Down-scheduling** | |
| **Benefits** | |
| Improved access to medicines | • Shortened time to treatment<br>• Increased treatment rates<br>• Reduced use of less effective or less safe non-pharmacological treatments or OTC medicines<br>• Improved adherence |
| Improved health outcomes due to improved access | • Shortened time to symptom relief<br>• Prevented disease onset<br>• Delayed or reduced disease progression |
| Improved public health | • Reduced externalities |
| Enhanced involvement by patients in their healthcare | • Increased responsibility<br>• Sense of empowerment<br>• Improved patient choice |
| Economic benefits of nonprescription medicines | • Decreased GP consultations<br>• Professional pharmacy resources better utilised<br>• Decreased healthcare costs from improved clinical outcomes<br>• Reduced patient time spent at GP consultations and filling prescriptions |
| **Risks** | |
| Poorer clinical outcomes | • Increased adverse events<br>• Increased risk of use in contraindicated populations<br>• Increased risk of interactions between medicines |
| Worsened health outcomes due to self-management | • Incorrect diagnosis and leakage to other indications<br>• Use of a less effective treatment<br>• Delay in seeking medical advice when symptoms continue or worsen |
| Intentional misuse with therapeutic intent | • Increased risk of over dosing due to inadequate efficacy or a belief that OTC medicines are less effective<br>• Increased risk of using the medicine for an extended period |
| Intentional overdose | • Increased risk of self-harm<br>• Increased risk of addiction |
| Accidental ingestion | • Increased risk of accidental ingestion by children |
| Economic risks of nonprescription medicines | • Increased medicine costs due to leakage to other indications<br>• Increased healthcare costs from worsened clinical outcomes<br>• Increased healthcare costs due to more frequent or severe adverse events<br>• Increased pharmacist time counselling patient |
| **Up-scheduling** | |
| **Benefits** | |
| Improved health outcomes due to GP advice | • Faster and more accurate diagnosis<br>• Reduced adverse events<br>• Reduced risk of use in contraindicated populations<br>• Reduced risk of interactions between medicines |

| Factors | Examples |
|---|---|
| | • Faster medical advice when symptoms continue or worsen |
| Intentional misuse with therapeutic intent | • Reduced risk of over dosing due to inadequate efficacy or a belief that OTC medicines are less effective<br>• Reduced risk of using the medicine for an extended period |
| Intentional overdose | • Reduced risk of self-harm<br>• Reduced risk of addiction |
| Accidental ingestion | • Reduced risk of accidental ingestion by children |
| Economic benefits of prescription medicines | • Reduced medicine costs due to leakage to other indications<br>• Reduced healthcare costs from improved clinical outcomes<br>• Reduced healthcare costs due to less frequent or severe adverse events<br>• Reduced pharmacist time counselling patient |
| **Risks** | |
| Reduced access to medicines | • Increased time to treatment<br>• Reduced treatment rates<br>• Increased use of less effective or less safe non-pharmacological treatments or OTC medicines<br>• Reduced adherence |
| Worsened health outcomes due to reduced access | • Increased time to symptom relief<br>• Increased disease onset<br>• Faster disease progression |
| Reduced public health | • Increased externalities |
| Reduced involvement by patients in their healthcare | • Increased reliance on GP advice<br>• Reduced sense of empowerment<br>• Reduced patient choice |
| Economic risks of prescription medicines | • Increased GP consultations<br>• Poorer utilisation of professional pharmacy resources<br>• Increased healthcare costs from worsened clinical outcomes<br>• Increased patient time spent at GP consultations and then filling a prescription |

Source: Adapted from Brass et al (2011) [9]

Typically health economic evaluations summarise the impact of interventions in terms of the impact on health outcomes and resource use, and thus costs. In contrast, the benefits of scheduling decisions may be in terms of improved health outcomes or decreased resource use, or both, while the risks may be in terms of reduced health outcomes or increased resource use, or both.

The following section discusses how to measure the impact of scheduling decisions on health outcomes and resource use. Note that approaches used to estimate the impact of re-scheduling a medicine on patient behaviour have been previously discussed in Section 2.3.2.

### 2.4.2. Measuring the impact on health outcomes

It is not possible to conduct an RCT to explore the impact of re-scheduling a medicine on health outcomes. Consequently, estimating the impact of scheduling decisions on health outcomes will largely rely on obtaining data from a variety of sources, which is then combined using economic modelling. Wherever possible, Australian studies are preferable. Otherwise whether data from other countries are applicable to the Australian setting should be assessed.

#### 2.4.2.1. Impact on health outcomes through treatment rates and choice of treatment

The natural history of the disease (i.e. health outcomes experienced if the patient chooses no treatment) needs to be estimated in order to measure the impact of changes in treatment rates and choice of treatment on health outcomes. Estimates of treatment effectiveness can then be applied to the natural history data in order to estimate the health outcomes experienced if the patient is treated, and by which treatment.

If the treatment effect relates to an immediate health outcome (e.g. proportion of patients who quit smoking) then it may be necessary to transform these to more patient relevant health outcomes using other data sources. For example, if the treatment effect relates to the proportion of patients who quit smoking, additional data will be needed to estimate the relationship between smoking and the risk of smoking-related diseases (e.g. lung cancer) and mortality. It may also be necessary to extrapolate health outcomes into the future if the follow-up period in the RCTs is relatively short (see Section 2.6).

Table 2-7 lists the different types of parameters that may be used to model health outcomes.

**Table 2-7: Types of health outcome parameters**

| Natural history | Treatment effectiveness |
|---|---|
| Continuous outcomes (e.g. cholesterol levels) | Change in levels or as a % |
| The probability of a certain event (e.g. probability of symptom relief, probability of quitting smoking, or probability of infection with influenza) | Odds ratios |
| The rate of events over a certain time period (e.g. migraines per month) | Change in levels or as a % |
| Time to event (e.g. time to symptom relief, or time to first cardiovascular event) | Hazard rate ratios |
| Continuous outcomes (e.g. cholesterol levels) | Change in levels or as a % |

The health outcomes for untreated patients can be estimated by using large, prospective, observational cohort studies, or by using the placebo arm of RCTs involving patients with the condition.

In comparison, treatment effectiveness is best informed by conducting a systematic literature review and meta-analysis of all relevant RCTs. The Population, Intervention, Comparator, Outcome (PICO) criteria and the search strategy should be clearly stated. Details regarding how to conduct systematic reviews and meta-analyses are available through the Cochrane Collaboration.[103] Systematic reviews and meta-analyses should be accompanied by a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, especially for key parameters such as efficacy parameters.[104, 105]

Down-scheduling a medicine increases the reliance on patients to independently recognise and assess symptoms, and choose whether to treat or seek medical advice.[9] Without medical advice, patients may incorrectly self-diagnose a condition as less severe than it actually is, or use an OTC medicine to treat symptoms which is less effective than a prescription medicine (e.g. due to the choice of medicine, route of administration, or due to the dose available OTC). Although this is not always the case. For example, pharmacists may refer a patient due to a medical practitioner due to the patient seeking the advice of a pharmacist, especially for Schedule 3 medicines, or due to the pharmacist using a screening tool. Finally, the availability of OTC medicines may also delay patients seeking medical advice when symptoms continue or worsen, especially if disease is asymptomatic.

To estimate the impact of self-management on health outcomes, data on the proportion of patients who no longer seek GP advice and switch treatments (discussed in Section 2.3) can be combined with estimates of the efficacy of each treatment option.

Note that these effects can be mitigated by making a medicine Pharmacist Only (Schedule 3), which enables the pharmacist to withhold supply of a medicine, providing pharmacist training and requiring the use of a screening tool (or administer a survey) before supplying an OTC medicine.

#### 2.4.2.2. Impact on health outcomes through time to treatment

For some medicines, treatment effectiveness may differ by the time elapsed between symptom onset and treatment. For example, oseltamivir is more effective if used early following the onset of influenza symptoms.[106]

The association between treatment effectiveness and the time-to-treatment is often explored as part of a phase II clinical trial or a post-market study. If there is a relationship, then the model may include multiple estimates of treatment effectiveness which differ by time-to-treatment, and the distribution of time-to-treatment if patients seek advice from a GP compared to using an OTC medicine. These data are likely to be obtained from patient surveys regarding the proposed medicine to be down-scheduled, for a similar medicine, or from overseas. If no evidence is available, the conservative assumption would be that re-scheduling a medicine does not improve the time to symptom relief.

#### 2.4.2.3. Impact on health outcomes through adherence

As noted earlier, for some medicines, treatment effectiveness may differ by the rate of adherence and persistence. For example, poor adherence to statins is associated with higher incidence of cardiovascular events and mortality.[107]

The association between treatment effectiveness and the rate of adherence or persistence can be estimated using two approaches:

1. If there are several RCTs reporting treatment effectiveness, then a meta-regression may be conducted using treatment effectiveness as the dependent variable and adherence rates as the explanatory variable. This approach may be limited by the number of RCTs available or a lack of variation in adherence rates across the RCTs.
2. Econometric analysis of patient-level data obtained from a RCT or observational data can be conducted using the outcome variable as the dependent variable and adherence rates as the explanatory variable, controlling for other observable confounders.

If no data are available, the conservative assumption is to assume that treatment effectiveness does not differ by the rate of adherence or persistence.

#### 2.4.2.4. Impact on health outcomes through adverse events

The number of treatment-related adverse events that occur is related to the number of patients treated, or the types of treatments received. There would be no change in the number of treatment-related adverse events if patients remain untreated or do not switch treatments.

The risk of an adverse event may be higher for some patients, such as those with contraindications or precautions or those concurrently treated with multiple medicines. If a medicine is down-scheduled then patients may not be aware or seek advice from a medical practitioner or pharmacist regarding whether they are at higher risk of adverse events. If this is the case, the proportion of patients with these factors and the risk of treatment-related adverse events for each sub-group (including those without any of the factors) needs to be estimated. Note that these effects can be mitigated by making a medicine Pharmacist Only (Schedule 3), which enables the pharmacist to withhold supply of a medicine, providing pharmacist training and requiring the use of a screening tool (or administer a survey) before supplying an OTC medicine.

Similar to estimating treatment efficacy, the risk of treatment-related adverse events is best informed by conducting a systematic literature review of all relevant RCTs (see Section 2.4.2.1). Alternatively the risk of treatment-related adverse events may be better estimated using large observational cohort studies if the adverse event is rare.[viii]

The association between treatment-related adverse events and contraindications or interactions can be estimated using two approaches:

1. If there are several RCTs reporting the risk of treatment-related adverse event, then a meta-regression may be conducted using treatment-related adverse events as the dependent variable and the rate of contraindications or interactions as the explanatory variable. This approach may be limited by the number of RCTs available or by the RCTs excluding these patients.
2. Econometric analysis of patient-level data obtained from a RCT or observational data can be conducted using the treatment-related adverse events as the dependent variable and contraindications or interactions rates as explanatory variables, controlling for other observable confounders.

Observational data can also be used to estimate the proportion of patients with contraindications or interactions (see Table 2-8).

**Table 2-8: Potential data sources used to estimate the incidence of adverse events**

| Parameter | Data sources |
|---|---|
| Probability of experiencing a treatment-related adverse event | • RCTs |
| | • Medical records |
| | • Patient surveys (e.g. if asked questions about adverse events, or linked to health administrative data) |
| Proportion of patients with contraindications or interactions | • Medical practitioner surveys (e.g. if asked questions about, for each patient treated or on average, what treatments they recommended or prescribed and pre-existing conditions) |
| | • Medical records |
| | • Patient surveys (e.g. if asked questions about current treatments and pre-existing conditions, or linked to health administrative data) |

RCT: randomised controlled trials

Adverse events may also arise due to subsequent treatments received. For example, if a patient uses a less effective method of contraception and gets pregnant, then the patient risks experiencing birth complications. Consequently, the risk of adverse events due to subsequent treatments received should also be estimated.

### *2.4.2.5. Impact on health outcomes through public health*

The use of some medicines may affect other individuals in the community. For example, the use of nicotine patches, increases smoking cessation, and thus reduces second-hand smoke inhalation and the incidence of diseases experienced by others. Or vaccination rates impact the risk of infection by non-vaccinated individuals.

Estimating these larger public health impacts requires estimating the rate of interactions between individuals in the community, infection rates given individuals have interacted and so on. These

[viii] It is unlikely that data from the TGA or FDA on post-market adverse events will be usable in the model because not all adverse events are reported (especially many years after product launch).

parameters are combined with estimates of treatment effectiveness using complex modelling approaches, such as susceptible-infected-recovered models (see Section 2.6).

#### 2.4.2.6. Impact on health outcomes through intentional misuse with therapeutic intent, accidental ingestion and intentional overdose

In Australia, there were 899 deaths from accidental poisoning from any substance in 2012, and 7,276 cases of poisoning by pharmaceuticals involving hospitalisation in 2012-13.[108, 109] Accidental poisoning by pharmaceuticals may be as a result of intentional misuse with therapeutic intent, intentional overdose, or accidental ingestion.

The severity of adverse events as a result of misuse or overdose (either accidental or intentional) is not the same for all medicines. An overdose of paracetamol may cause liver damage and death[110], while an overdose of omeprazole may cause temporary symptoms like nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache.[111] The duration of use – short term versus long term – is also an important factor which determines the risk and severity of adverse events.

Consequently, the impact on health outcomes as a result of misuse or overdose (either accidental or intentional) is dependent on the properties and duration of use of the medicine(s) under consideration.

***Intentional misuse with therapeutic intent***

In some cases, intentional misuse with therapeutic intent occurs when patients exceed the recommended dose if the response to treatment is perceived to be inadequate. This is more likely to occur in the case of medicines that are indicated to treat acute symptoms, such as pain. In other cases, patients may exceed the indicated duration of use instead of seeking medical advice when symptoms persist. Conversely, intentional misuse is highly unlikely in the case of medicines where the therapeutic response is not immediately observable, such as vaccines, contraceptives, and statins.

Other factors that may affect overdosing include the failure to read label instructions, poor comprehension of label instructions, and failure to recognize the active ingredient and simultaneously taking more than one product containing the same active ingredient (or in the same therapeutic class).

The risk of intentional misuse with therapeutic intent before re-scheduling a medicine may be estimated using:

- A patient survey, where patients are asked about the last dose they took, the average dose taken, or maximum daily dose used, and the duration of treatment.
- Administrative data on the number of hospitalisations due to accidental poisoning with the medicine, compared to estimates of the number of medicines prescribed or purchased.

Re-scheduling a medicine may impact the pattern of overdoses. This will be dependent on the number of patients switching from no treatment to treatment, or switching between medicines. Re-scheduling a medicine may also impact overdose patterns by changing patient behaviour. For example, patients may not seek clinical advice following the down-scheduling of a medicine or they may have the view that a medicine is safer or less effective because it is available OTC.

The risk of overdoses may be mitigated by scheduling the medicine as Pharmacist Only (Schedule 3) to ensure mandatory counselling by a pharmacist, while the severity of overdoses may be mitigated by reducing pack sizes for OTC medicines compared to if the medicine is prescribed. In fact, the overall impact on health outcomes may be improved by down-scheduling if the reduction in the severity of overdoses is large enough.

The impact of re-scheduling a medicine on the risk of intentional misuse with therapeutic intent can be estimated using observational data on overdoses before and after schedule changes for similar medicines or medicines in another country. For example, in Australia in 2012-13 there were 863 hospitalisations to treat accidental poisoning due to exposure to paracetamol in Australia.[109] Around 93% of these hospitalisations were of adults and 20% were due to therapeutic overdose (75% were for self-harm).[ix][110] Over the same period (2012-2013) there were 9.7 million PBS prescriptions for paracetamol, or around 877 million tablets, and around 1,884 million OTC tablets containing paracetamol (adult formulations) sold.[x] [110, 112, 113] Consequently the risk of serious therapeutic overdose of adults with paracetamol was six per 100 million tablets consumed. Of these overdoses, there were around three deaths[xi][110, 113], thus the risk of death of adults due to therapeutic overdose with paracetamol was 0.3 per 100 million tablets consumed.

Alternatively, threshold analysis could be conducted on this parameter to see the extent of change in the risk of intentional misuse that is required for the scheduling change to not be cost-effective (see Section 2.7.2).

Label comprehension studies may also be informative to estimate the risk of overdosing following a scheduling change.

### *Intentional overdose*

Rather than using a medicine to treat a condition, patients may use more than the recommended dose for self-harm. Again, this is highly dependent on the properties of the medicine. Benzodiazepines, paracetamol and antidepressants comprise 89% of the medicines or drugs used in hospitalisations as a result of intentional self-harm due to exposure to poisons (except for gas) in 2010-11 (see Table 2-9). Note that benzodiazepines and antidepressants are both prescription-only medicines. While down-scheduling a medicine may increase its availability, it may not increase the number of patients attempting to self-harm with that medicine.

**Table 2-9: Medicines/drugs involved in hospitalisations as a result of intentional self-harm due to exposure to poisons (except gas), Australia, 2010–11**

| Drugs, medicaments and biological agents | Hospitalisations | % of total |
|---|---|---|
| Psychotropic drugs, NEC | 8,872 | 43% |
| - Antidepressants | 5216 | 25% |
| Antiepileptic, sedative-hypnotic and anti-parkinsonism drugs | 8523 | 42% |
| - Benzodiazepines | 7158 | 35% |
| Non-opioid analgesics, antipyretics and anti-rheumatics | 7042 | 34% |
| - Paracetamol | 5915 | 29% |
| Narcotics and psychodysleptics [hallucinogens] | 3764 | 18% |
| - Other opioids (codeine, morphine) | 2849 | 14% |
| Primarily systemic and haematological agents | 1243 | 6% |
| Drugs primarily affecting the cardiovascular system | 783 | 4% |
| Drugs primarily affecting the autonomic nervous system | 671 | 3% |
| Hormones and their synthetic substitutes and antagonists, NEC | 612 | 3% |

[ix] Based on an analysis of hospital admissions for accidental poisoning with paracetamol in Victorian hospitals from 1987-88 to 2000-01.
[x] Based on 1,596 million OTC tablets containing paracetamol (adult formulations) sold in 2001, adjusting for population growth.
[xi] Between 1989 to June 1995 there were four deaths with paracetamol alone in Victoria, or around three deaths Australia wide in 2012-13, account for population growth and assuming the rate of deaths in Victoria is similar in other states.

| Drugs, medicaments and biological agents | Hospitalisations | % of total |
|---|---|---|
| Systemic antibiotics | 344 | 2% |
| Drugs primarily affecting the gastrointestinal system | 292 | 1% |
| Other and unspecified drugs, medicaments and biological substances | 1034 | 5% |
| **Total** | **20,499** | |

Note: Patients may use more than one medicine/drug.
NEC: Not elsewhere classified.
Source: [114]

In addition to treating symptoms of a disease, some medicines produce pleasant side-effects, such as feelings of euphoria, or may be addictive. Down-scheduling these medicines increases their availability and so may unintentionally increase their use, by patients with and without the condition. Increased use may result in unintentional overdoses, resulting in hospitalisation and potentially death. The approach to estimating hospitalisations and deaths due to unintentional overdoses is the same as intentional misuse with therapeutic intent, as described above.

Overall, not all economic evaluations of re-scheduling a medicine will include the impact of intentional overdoses. Whether it is included should be considered on a case-by-case basis.

### *Accidental ingestion*

Parents may discount the risks of OTC medicines compared to prescription medicines, and so may be less attentive to the risks of accidental ingestion by children.[9] In Australia the rate of poisoning of children by pharmaceuticals is very low and has halved since 1999-2000.[109] In 2012-13 there were no deaths from accidental poisoning among those aged under 15 years, and 1,025 and 1,146 cases of poisoning by pharmaceuticals involving hospitalisation in children aged 0-4 years and 5-14 years, respectively.[115] It is estimated that around 95% of all accidental poisoning of children aged under five years is due to unintentional ingestion.[116] Table 2-10 presents the agents involved in pharmaceutical poisoning hospitalisations of children and young people aged less than 24 years.

**Table 2-10: Pharmaceutical poisoning hospitalisations of children and young people, Australia, 2012-13**

| Poisoning by | Hospitalisations | % of total |
|---|---|---|
| Non-opioid analgesics, antipyretics and anti-rheumatics | 3,935 | 37.1 |
| Psychotropic drugs | 3,174 | 29.9 |
| Antiepileptic, sedative-hypnotic and anti-parkinsonism drugs | 1,329 | 12.5 |
| Narcotics and psychodysleptics (hallucinogens) | 619 | 5.8 |
| Diuretics and other and unspecified drugs, medicaments and biological substances | 298 | 2.8 |
| Primarily systemic and haematological agents | 232 | 2.2 |
| Agents primarily affecting the cardiovascular system | 226 | 2.1 |
| Hormones and their synthetic substitutes and antagonists | 195 | 1.8 |
| Drugs primarily affecting the autonomic nervous system | 168 | 1.6 |
| Topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinolaryngological and dental drugs | 113 | 1.1 |
| Anaesthetics and therapeutic gases | 112 | 1.1 |
| Systemic antibiotics antirheumatics | 85 | 0.8 |
| Agents primarily acting on smooth and skeletal muscles and the respiratory system | 64 | 0.6 |

| Poisoning by | Hospitalisations | % of total |
|---|---|---|
| Agents primarily affecting the gastrointestinal system | 47 | 0.4 |
| Other systemic anti-infectives and antiparasitics | 23 | 0.2 |
| **Total** | 10,620 | |

Source: [109]

Due to accidental ingestion being rare, the risk of accidental ingestion before down-scheduling is best estimated using administrative data on the number of hospitalisations due to accidental poisoning in children under five years, compared to estimates of the number of medicines prescribed.

Down-scheduling may impact accidental ingestions with the medicine, dependent on the number of patients switching from no treatment to treatment with the down-scheduled medicine, or between medicines. Down-scheduling may also impact accidental ingestions by changing patient behaviour, for example by not safely securing the packs. The severity of adverse events due to accidental ingestion may be minimised using smaller packs for OTC medicines. The impact on accidental ingestions can be estimated based on observational data on overdoses before and after down-scheduling for similar medicines or medicines in another country (see Section 2.3.2.2), however given its rarity it is unlikely that this impact will be able to be estimated.

Overall, not all economic evaluations of re-scheduling a medicine will include the impact of accidental ingestion. Whether it is included should be considered on a case-by-case basis.

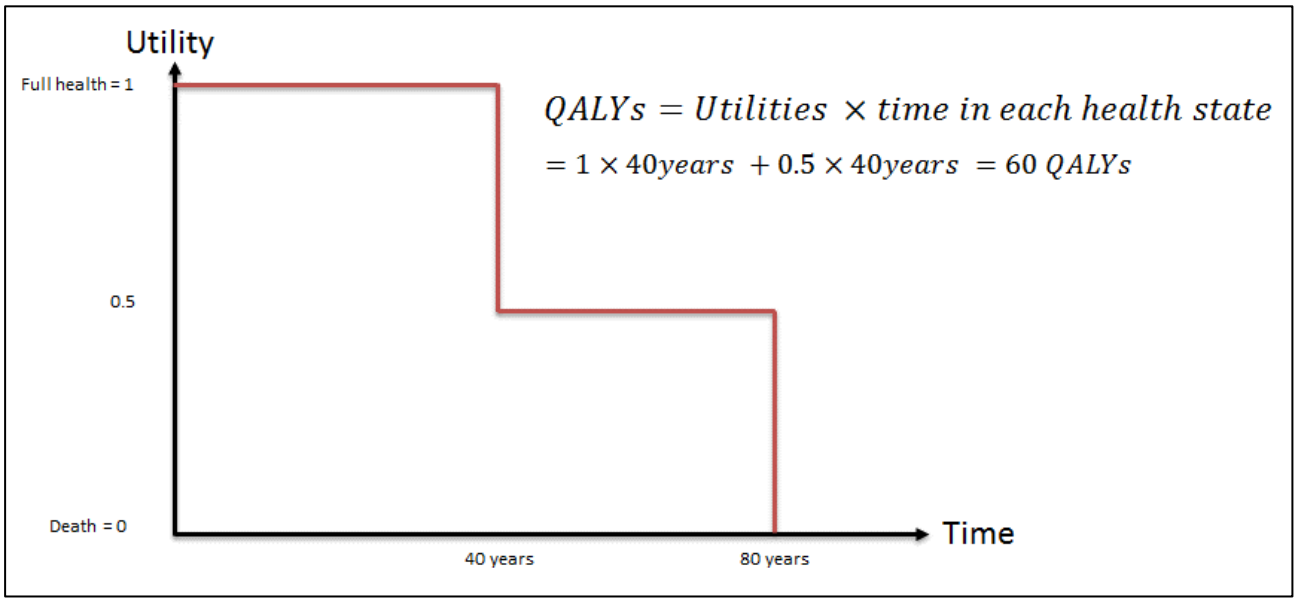
### 2.4.3. Valuing the impact on health outcomes

Re-scheduling a medicine may have a short term impact on symptoms, but may also have a longer term impact on disease incidence and disease progression. It may also increase or decrease the incidence of a range of adverse events. As a result, re-scheduling a medicine may impact both quality of life and survival. Providing decision makers with a list of the different impacts of scheduling decisions on a wide range of health outcomes can be overwhelming. Decision makers may also find the results difficult to interpret, especially if re-scheduling improves some health outcomes but makes others worse.

As a result, decision makers, such as the Pharmaceutical Benefits Advisory Committee, prefer health outcomes to be measured using QALYs.[19] QALYs are also suggested by the Office of Best Practice for use in Regulatory Impact Statements.[22]

QALYs incorporate survival and quality of life in a single measure.[117] QALYs are calculated by multiplying the number of years lived in each health state by a 'utility value' or 'utility weight' for each respective state. Utilities are estimated based on the strength of preferences across different health states on a cardinal scale from zero (death) to one (health). A negative utility values represents states worse than death. A disutility value is a small decrement applied to a utility value. Figure 2-3 provides an example of how to calculate QALYs using utilities.

**Figure 2-3: Diagrammatic representations of utilities and QALYs**




QALY: Quality Adjusted Life Year

Utility values should ideally be based on the measured strength of preference between health states, which are measured using methods that require respondents to trade-off between survival and quality of life. The two key methods are:

- Standard gamble, where individuals[xii] are asked to choose between two alternatives: one where the individual will either experience perfect health for ten years with probability *p* or immediately die with probability *1-p*; and another where they have the certain outcome of living in a particular health state for ten years. Individuals are then asked at what value of *p* they are indifferent between the two alternatives. The utility value is thus estimated as *p*.[117]
- Time trade-off, where individuals[xiii] are asked to choose between two alternatives: one where the individual will experience perfect health for *t* years; and another where they live in a particular health state for ten years. Individuals are then asked at what value of *t* they are indifferent between the two alternatives. The utility value is thus estimated as *t/10*.[117]

Completing a standard gamble or a time trade-off survey can be cognitively burdensome to patients. Instead patients may be surveyed using a multi-attribute utility instrument (MAUI) in order to minimise this burden and facilitate the estimation of utility values.[117] A MAUI allows patients to describe the health state they are currently experiencing, and then a preference-based algorithm is used to convert the health state described by patients into utility values. Algorithm have been developed by surveying individuals about their preferences regarding a set of health states through a MAUI using time trade-off or standard-gamble methods.

The PBAC guidelines stipulate that it is preferable utilities are measured within an RCT.[19] However, in the case of re-scheduling medicines it is not possible to conduct RCTs as it is a nation-wide policy decision. Consequently, utility values may be obtained from other studies.

A systematic review of the published literature may be conducted to identify relevant studies measuring utility values. Guidelines have been developed regarding how to conduct such systematic reviews.[118]

[xii] Patients with regards to their current health state, or the general population with health states described using vignettes.
[xiii] As above.

These guidelines are summarized in Box 2-5, however with the Assessment of Quality of Life (AQOL) instrument added.[119]

In addition to these databases, it may also be worth searching for the condition, disease or adverse event in the Cost-effectiveness Analysis Registry.[120]

**Box 2-5: Search strategy for utility values**

**Databases:** MEDLINE, EMBASE, CENTRAL

**Search terms (keywords):**
Condition/disease/adverse event
AND
quality adjusted life
OR
quality-adjust-life
OR
(qaly$ or qald$ or qale$ or qtime$)
OR
disability adjusted life
OR
daly$
OR
(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
OR
(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
OR
(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
OR
(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D)
OR
(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
OR
(euroqol or euro qol or eq5d or eq 5d)
OR
(hql or hqol or h qol or hrqol or hr qol)
OR
(hye or hyes)
OR
(health$ year$ equivalent$
OR
utility$
OR
(hui or hui1 or hui2 or hui3)
OR
disutiliti$
OR
rosser
OR
quality adj2 wellbeing
OR

qwb
OR
standard gamble$
OR
sg
OR
time trade off
OR
time tradeoff
OR
tto
OR
(aqol or aqol8D or aqol6D or aqol7d or aqol4D or aqol 8D or aqol 6D or aqol 7d or aqol 4D)

**Potential limits:** English

**Date**: Date of data base and when the search was conducted.

**Inclusion criteria:** Used techniques such as time trade-off or standard gamble to elicit utility values, or used a MAUI, such as the EQ-5D, HUI3, SF-6D, Rosser-Kind index, QWB

**Exclusion criteria**: Abstracts and reviews.

$ = truncation (in some databases this is *) e.g. utility$ searches for utility or utilities
Adj = adjacency operator. E.g. adj2 = within two words of each other.
Source: [118]

In addition to assessing whether the health state is representative of that required for the economic evaluation (e.g. type and severity of symptoms), the methods should be described and assessed for validity. See Table 2-11 for guidelines.

**Table 2-11: Key criteria to consider in quality assessment of studies estimating utilities**

| Criteria | Consideration |
|---|---|
| Sample size | The precision of the estimate should be reflected in the variance around any estimate used in the model |
| Respondent selection and recruitment | Does this result in a population comparable to that being modelled? |
| Inclusion/exclusion criteria | Do these exclude any individuals? |
| Response rates to instrument used | Are the response rates reported and if so, are the rates likely to be a threat to validity? |
| Loss to follow-up | How large is the follow up and are these reasons given? Are these likely to threaten the validity of the estimates? |
| Missing data | What are the levels of missing data and how are they dealt with? Again could this threaten the validity of the estimates? |
| Any other problems with the study | For example, relevance of location? |
| Appropriateness of measure | Is the measure used valid in the group of patients (e.g. e.g. MAUI, scenario-based using a time trade-off or standard gamble survey)? |

Source: [118]

When selecting utility values, it is preferable that respondents are patients, carers or the general population (e.g. not healthcare professionals). It is also preferable that utility values are obtained from the same study, or utility values are estimated using similar methods and populations when obtained

from different studies. Finally, sensitivity analysis should be conducted if there is more than one acceptable source of utility values for the same health state identified (see Section 2.7.2).

## 2.4.4. Measuring the impact on resource use

Re-scheduling a medicine will have a direct and immediate impact on GP consultations to obtain prescriptions and medicine costs. It is also important to consider the impact on other healthcare resources resulting from the subsequent impact on health outcomes, such as delayed disease onset or progression, adverse events, and misuse[xiv].

### *2.4.4.1. GP consultations*

Down-scheduling a medicine will reduce GP consultations in order to obtain a prescription, while up-scheduling a medicine will increase GP consultations. The maximum potential reduction or increase is dependent on the number of GP consultations where a prescription was or will be obtained, which is determined by pack size (e.g. number of tablets), number of repeats per prescription, and the duration of treatment. Not all patients will switch to obtaining a medicine OTC following down-scheduling, and may continue to seek advice from the GP regarding treatment for their condition. Similarly, not all patients will switch to obtaining a prescription following up-scheduling, and may switch to using another OTC medicine or ceasing treatment. Furthermore, untreated patients may be referred for medical review when seeking treatment from the pharmacist (as is expected with erectile dysfunction medicines(32)).

In estimating the impact of re-scheduling a medicine it is also necessary to consider that patients may obtain prescriptions for the down-scheduled medicine as part of a GP consultation for other reasons, including different conditions and prescriptions for other medicines used to treat the same condition. For example, in Australia in 2014-15 around 1.6 problems were managed per GP consultation.(121) Consequently, the number of GP consultations will not necessarily fall by the number of GP consultations where a prescription was obtained.

Four approaches may be used to estimate the reduction in GP consultations from re-scheduling a medicine:

1. Surveying currently treated patients or GPs regarding the proportion of GP consultations that solely involved obtaining a prescription for the medicine.
2. Estimating the proportion of prescriptions obtained and dispensed on the same day using PBS data.
3. Adjusting the number of GP consultations required for a prescription by the average number of problems managed per GP consultation. For example, if three consultations per year would be required and 1.6 problems are managed per GP consultation, then it is estimated that 1.8 GP consultations would continue to be needed per year, or 1.2 GP consultations would be avoided.
4. Estimating the impact on GP consultations where a certain problem was managed when the schedule of a similar medicine was changed in Australia using linked Medicare Benefits Scheme (MBS) and PBS data.

Changes in healthcare resource use in another country may not necessarily be observed in Australia due to differences in healthcare systems or for cultural reasons. Consequently, published data on the impact

[xiv] This includes intentional overdose (e.g. use of more than the recommended dose for self-harm), intentionally misuse with therapeutic intent (e.g. use of more than the recommended dose due to perceived inadequate efficacy or a belief that OTC medicines are less effective, or using the medicine for an extended period), and accidental ingestion (e.g. non-intentional use of a medicine, usually by a child).

on GP consultations observed in another country when the schedule of a medicine was changed may not be applicable to the Australian setting.

#### 2.4.4.2. Pharmacist time

Re-scheduling a medicine may change the amount of pharmacist time involved in counselling the patient regarding the appropriate treatment, or administering a patient-screening questionnaire. The impact of re-scheduling a medicine on pharmacists' time could be estimated by surveying patients regarding the average time taken to counsel patients with the condition, or by conducting a pilot where medicines are dispensed.

#### 2.4.4.3. Other resource use

Re-scheduling a medicine is likely to impact the usage pattern of different medicines used to treat the same condition, and may also affect adherence. Approaches used to estimate the impact of down-scheduling on switching and adherence are discussed in Section 2.3.2.

Re-scheduling a medicine will also impact subsequent usage of medicines and other resources, for example, due to changes in longer-term health outcomes or treating adverse events. The impact on other healthcare resources may include, but are not limited to: hospitalisations, emergency department visits, specialist consultations, outpatient visits, imaging, pathology tests, and allied healthcare visits.

Resource usage from these health outcomes may be estimated using:

- Health administrative data;
- Patient surveys (e.g. if asked a question about current treatments, or linked to health administrative data);
- Medical practitioner surveys (e.g. if asked a question about, for each patient treated or on average, what treatments they recommended or prescribed); and
- Medical records.

Other studies estimating resource usage associated with each health outcome are also likely to have been published. Note that published data from another country may not be applicable to the Australian setting.

When data are not available, parameter values may be elicited from experts (see Section 2.3.1.2) or assumptions may be made (see Section 2.3.1.3).

When re-scheduling a medicine results in reducing the incidence of a disease, it is more efficient to identify studies that estimate the average healthcare cost of these diseases in Australia, rather than estimating resource use for each step of the disease from incidence to death.

### 2.4.5. Valuing the impact on resource use

The unit cost applied to each resource used should represent its opportunity cost. When market prices are available and the market is reasonably competitive, the market price is a reasonable approximation of the opportunity cost. However, in healthcare this may not be the case as the market is highly regulated. In Australia, one of the best guides to how to value resource use is the 'Manual of Resource Items and their Associated Costs'.[122]

All unit costs should relate to the same price year (e.g. 2016 Australian dollars). If required, the Australian Institute for Health and Welfare (AIHW) health price index should be used if inflating costs.[123] As a general rule, unit costs should not be inflated into the future because there is no guarantee they will

increase (e.g. the price of health technologies may decrease over time or the health system may become more productive).

#### 2.4.5.1. Medical services unit costs

The unit cost of medical services (including GP, specialist and anaesthesia consultations, imaging tests, and pathology tests) can be based on the MBS.[124] The entire MBS fee is generally not reimbursed, except for in the case of GP consultations. Instead 85% of the MBS fee is reimbursed for out-of-hospital medical services, while 75% of the MBS fee is reimbursed for in-hospital medical services provided to private patients. If the patient has private health insurance, the patient is further reimbursed by the private health insurance company the difference between the MBS fee and 75% of the fee (i.e. 'the gap').[xv] However, medical practitioners are not required to charge patients the MBS fee – they may charge above or below this amount[xvi]. It is recommended that the entire MBS fee when valuing medical services as a proxy for the expected amount charged to patients[122], unless information on the exact amount charged to patients is known.

#### 2.4.5.2. Medicine unit costs

The unit cost of most medicines can be based on the PBS schedule.[125] In particular, the dispensed price for maximum quantity (DPMQ)[xvii] is the agreed price to be reimbursed to pharmacies for dispensing pharmaceuticals listed on the PBS between the Australian Government Department of Health and manufacturers (minus any patient co-payments paid to pharmacies). Pharmacies cannot charge over this amount.

Many OTC medicines are not listed on the PBS schedule. In this case, unit costs may be obtained from online pharmacies or by surveying pharmacies.

#### 2.4.5.3. Pharmacist time cost

The unit cost of pharmacist time can be estimated using the hour pay rate in the Pharmacy Industry Award.[126] It is likely that an experienced pharmacist or pharmacist in charge is more likely to be involved in patient counselling or administering a patient-screening questionnaire, rather than a pharmacist assistant or, student or intern. This is especially the case if additional pharmacist training is required in order to be allowed to supply a newly down-scheduled medicine. Economic evaluations are concerned with the marginal impact on resources. Consequently, pharmacist overhead costs do not need to be estimated and apportioned to each medicine supplied or dispensed, unless the impact on pharmacist time is substantial (i.e. overheads such as rent, electricity etc will be the same regardless of the schedule of a medicine).

#### 2.4.5.4. Admitted hospitalisations and emergency department unit costs

The unit cost of hospitalisations and emergency department visits can be based on the National Hospital Cost Data Collection.[127] The average cost per Australian Refined Diagnosis Related Groups (AR-DRG) should be used, which takes into account the average length of stay. The AR-DRG most likely to be used for hospital admissions may be based on expert opinion. A weighted average, based on the number of separations, may be used where multiple AR-DRGs are likely (e.g. with and without complications). The

[xv] Private health insurance does not cover out-of-hospital medical services, such as specialist visits.
[xvi] If the fee charged is equal to the amount reimbursed by the DoH it is referred to as "bulk billing".
[xvii] Another approach is required for drugs available in the form of vials and administered intravenously, however these drugs are unlikely to be used.

National Hospital Cost Data Collection also reports the unit cost per admitted and non-admitted emergency department visits.

Note the potential to double-count hospitalisation costs in public hospitals with those obtained from other sources (e.g. MBS and PBS) due to the AR-DRG for public hospitals includes all costs incurred during hospitalisation.

#### 2.4.5.5. Prostheses and blood products

The cost of blood products is available on the National Blood Product List[128], while the cost of all prostheses (e.g. screws and rods) used in orthopaedic surgery is available on the Prosthesis List.[129]

### 2.4.6. Measuring and valuing the impact on other outcomes

Re-scheduling a medicine may also have additional impacts that are not reflected in changes in health outcomes, such as the impact on responsibility, sense of empowerment, reliance on GP advice, and patient choice.

The value an individual places on these impacts can be estimated using a discrete choice experiment. For example, the value of improved patient choice can be estimated by including an attribute relating to choice, in addition to other attributes reflecting other aspects of the treatment pathway, such as efficacy, risk of adverse events, time to treatment and so on.[130] See Section 2.3.2.4 for discussion of how to conduct a discrete choice experiment.

## 2.5. Types of analysis

Four different types of analysis are often used in economic evaluation of health interventions: cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis. A summary of the different types of analysis are summarized in Table 2-12. The type of analysis is largely dependent on the impact of the health intervention on health outcomes and how the health outcomes are measured and valued.

If the health intervention is found to be equally effective and equally safe as the comparator(s) then a cost-minimisation analysis is the most appropriate approach. In this case, only costs are estimated and compared and the economic evaluation aims to identify which treatment is the least costly. However, this approach cannot be used to compare treatments when one is more/less effective or safer than another.

In the context of scheduling decisions, there is likely to be both positive (e.g. due to reduced time to treatment) and negative (e.g. due to adverse events) impacts on health outcomes. Cost-minimisation analysis is unlikely to be adequate and one of the other analyses should be conducted.

Cost-effectiveness analysis involves measuring the health outcomes using a single effect of interest, common to both treatments but achieved to different degrees (e.g. reduction in pain) while cost-utility analysis is one where the health outcomes are measured using QALYs. For both these analyses health gained and additional costs are summarized using an ICER (see Section 2.6.4). How to interpret the results of these analyses is discussed in Section 2.8.

Cost-benefit analysis involves the additional step of valuing the health outcomes (e.g. QALYs) in monetary terms (e.g. by multiplying by some value per QALY). This is done by using a human capital approach, a stated willingness to pay approach, or a revealed preferences approach based on the willingness to pay to reduce the risk of death by purchasing a product, or the additional amount paid to workers undertaking risky work.[131] Under a cost-benefit analysis approach, the net benefit of each

treatment is compared and the economic evaluation aims to identify which treatment has the highest net benefit. However, it can be difficult and is often controversial to place a monetary value on health outcomes, and as such it is rarely used when a treatment or program affects health outcomes.

In the context of scheduling decisions, it is recommended that cost-utility analysis should be conducted as it can incorporate the positive and negative impacts on a range of health outcomes.

**Table 2-12: Types of analysis**

| Type of Analysis | Measurement of health outcome | Output | Decision | Strengths | Weaknesses |
|---|---|---|---|---|---|
| Cost-minimisation analysis | Equal efficacy<br>Note: no evidence of efficacy ≠ equal efficacy | Cost ($) | Which is the least costly? | • Simple | • Cannot compare interventions when one is more effective and more costly, or when > 1 health outcome or adverse events |
| Cost-effectiveness analysis | Single effect of interest, common to both interventions but achieved to different degrees (e.g. lung cancer cases avoided) | Cost ($) per unit of health gained (e.g. lung cancer cases avoided) | Which is the most cost-effective? | • Relatively simple<br>• Can compare interventions when one is more effective and more costly | • Difficult to interpret<br>• Health outcomes not always patient relevant<br>• Cannot compare interventions when > 1 health outcome or adverse events |
| Cost-utility analysis* | QALYs gained | Cost ($) per QALY gained | Which is the most cost-effective? | • Easier to interpret and make decisions<br>• Health outcomes patient relevant (quality of life and survival)<br>• Can compare across a wide range of interventions and diseases (allocative efficiency)<br>• Incorporates preferences across health states | • Difficult to estimate utility values<br>• Ethical considerations |
| Cost-benefit analysis | Monetary units ($) | Net benefit ($) | Which has the highest net benefit? | • Easy to understand<br>• Can compare across a wide range of interventions and diseases (allocative efficiency)<br>• Can answer question about whether an intervention increases social welfare | • Difficult and controversial to place a monetary value on health outcomes<br>• Ethical considerations<br>• Rarely used when a intervention affects health outcomes |

* In the context of scheduling decisions, it is recommended that cost-utility analysis should be conducted as it can incorporate the positive and negative impacts on a range of health outcomes.
QALY: quality adjusted life year.

# 2.6. Summarising data

Due to the need to draw on a range of sources, economic evaluations of scheduling decisions will inevitably involve synthesising estimates from these sources using an economic model.

## 2.6.1. Structuring an economic model

The structure of an economic model depends on the nature of the treatment and the disease it is being used to treat. For example, whether the disease is acute or chronic, whether the risk of events (including treatment effectiveness) changes over time, and whether the risk of events is dependent on what happened to the patient in the past.[11] In general, there are two types of economic models: decision trees and state transition models.

In the context of scheduling decisions, the economic model will initially be a decision tree that reflects how re-scheduling a medicine changes patient behaviour (Part A) (see Figure 2-1 for an example of the decision tree). Following on from the patient's choice of each treatment is attached a decision tree or a state transition model, which reflects the impact of the treatment on health outcomes and resource use (Part B). It is recommended that a systematic literature review is conducted to identify economic evaluations of the cost-effectiveness of funding the medicine, as it may help develop the structure of Part B of the model.

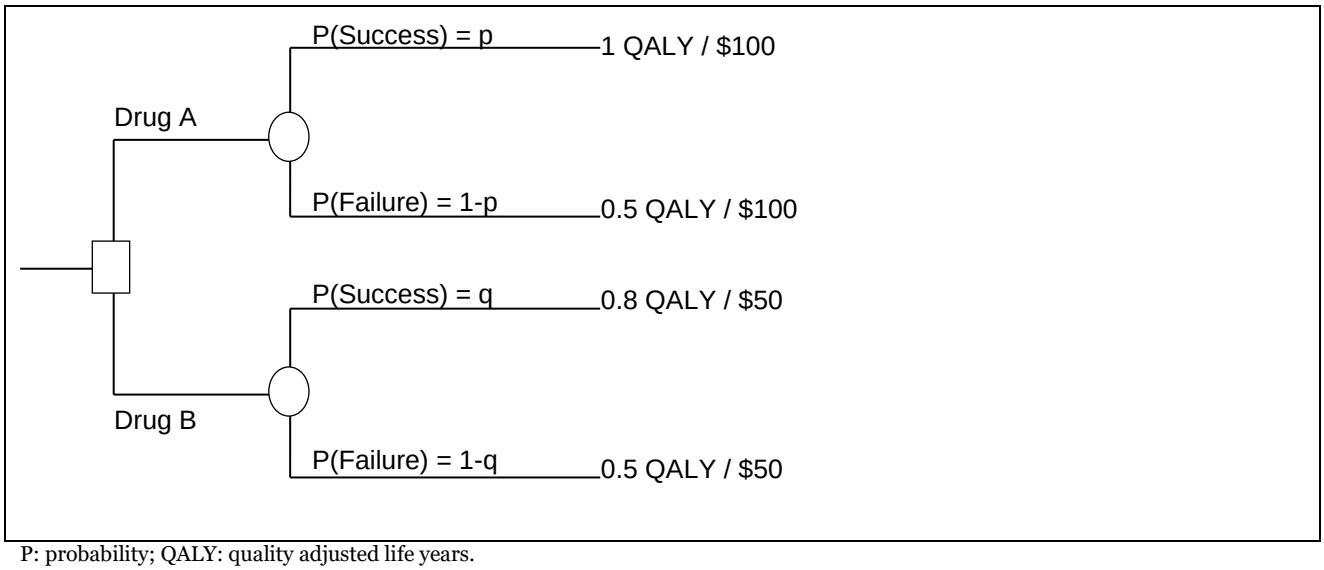
The structure of the model should be clearly described, with diagrams of the model provided, and justified. If a state transition model is provided, the health states and cycle lengths should be reported.

### *2.6.1.1. Decision trees*

A decision tree is the simplest type of model.[132] Decision trees contain pathways following a treatment decision. Each pathway results in a possible health state, which is associated with health outcomes and costs (also known as "payoffs"). Each pathway is associated with transition probabilities that determine whether the health state will occur. The health outcomes, costs and probabilities may differ for each possible treatment. For each treatment option, the expected health outcomes are estimated by weighting the health outcomes associated with each pathway by the probabilities. A similar approach is taken for costs.

Figure 2-5 presents a diagrammatic representation of a decision tree.

**Figure 2-4: Diagrammatic representation of a decision tree**



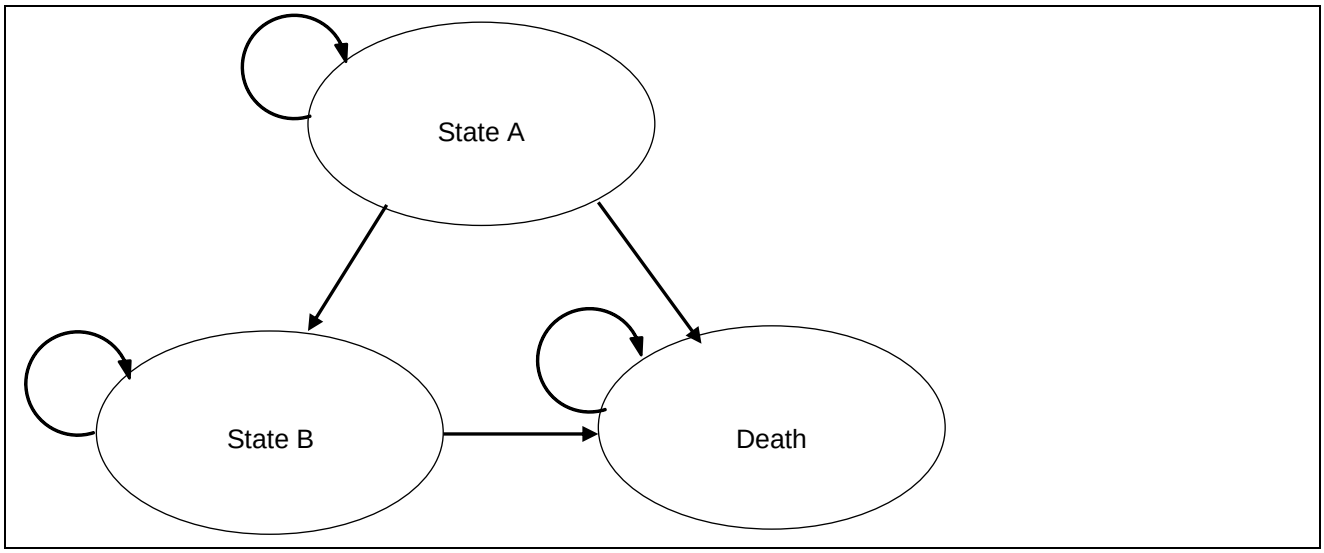

P: probability; QALY: quality adjusted life years.

### 2.6.1.2. State transition models

State transition models characterises a disease in terms of health states experienced by patients and how patients transition between the health states over a series of discrete time periods (called "cycles").[12] Health outcomes and costs are accrued each cycle, depending on their current health state. Once-off health outcomes and costs may also be accrued when they move between health states (e.g. due to events). The transition probabilities, health outcomes, and costs may also differ for each possible treatment. State transition models that treat all patients in a particular health state as similar in terms of their transition probability are referred to as cohort or Markov models. Tunnel states can be used to model changes in the risk of events dependent on what happened to the patient in the past. Alternatively, microsimulation models and discrete event simulation may be used, which can model changes in the risk of events dependent on what happened to the patient in the past. Susceptible-infected-recovered models may be more appropriate for infectious diseases and vaccines, which can model changes in the risk of events dependent on the health state of individuals.

Figure 2-5 presents a diagrammatic representation of a state transition model.

**Figure 2-5: Diagrammatic representations of a state transition models**




## 2.6.2. Transition probabilities

Transition probabilities determine the movement of patients between health states in a model. Transition probabilities are likely to be obtained from a variety of sources, which are described in Sections 2.3 and 2.4. However, if the follow-up in the data sources used is relatively short then it may also be necessary to extrapolate health outcomes into the future. This can be done using a Markov model or by fitting parametric functions to Kaplan-Meier survival curves. Guidelines are available regarding how to identify the most appropriate parametric functions.[21]

## 2.6.3. Discount rates

In economic evaluations, costs and health outcomes should be discounted so that they are valued in present terms. The key reason is because society prefers to benefit sooner rather than later. Consequently, the discount rate should reflect society's real time preference (e.g. excluding market risk). The PBAC guidelines recommends 5% per annum, while the Office of Best Practice Regulation recommends 7%.[19, 22]

## 2.6.4. Incremental cost-effectiveness ratio (ICER)

The results of the economic evaluation are summarized using an ICER. The ICER for re-scheduling a medicine in terms of cost per QALY gained is calculated as follows:

$$ICER = \frac{Cost_{Schedule\ changed} - Mean\ Cost_{Scheduled\ unchanged}}{QALYs_{Scheduled\ changed} - Mean\ QALYs_{Scheduled\ unchanged}}$$

Thus the output of a cost-effectiveness analysis is additional cost per unit of health gained (e.g. cost per 1-point reduction in pain) and the output of a cost-utility analysis is additional cost per QALY gained.

## 2.6.5. Model validation

Various techniques can be used to validate the structure of the model, including:

- Face validity testing of the model structure, parameter values and outcomes using experts;
- Comparing the model structure, parameter values and outcomes to other models in the published literature;
- Testing the model for any mistakes using external review, extreme value testing etc; and
- Comparing the model health outcomes before down-scheduling to empirical data (e.g. number of hospitalisations for adverse events).

The Assessment of the Validation Status of Health Economic decision models (AdViSHE) tool should be used as a guide to validate the economic model.[20]

All economic evaluations should be accompanied by a Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist to ensure transparency in the methods and to allow decision makers to assess the quality of the economic evaluation.[17]

# 2.7. Understanding uncertainty

## 2.7.1. Why understanding uncertainty is important

Scheduling decisions are often based on limited data, especially regarding patient behaviour, the risk of adverse events and possible benefits. Decision makers have long recognised the negative risks of down-scheduling. In response to limited data, some authors have claimed that the TGA has increasingly taken a risk-adverse approach to decision making.[7, 35] However, it is important to differentiate between the presence of uncertainty compared to the risk of making an inappropriate scheduling decision.

If down-scheduling is not cost-effective but is implemented, patients may experience poorer health outcomes (e.g. due to adverse events) and resources (e.g. used to treat adverse events) may be diverted from treating other patients. However, if down-scheduling is cost-effective but not implemented, patients' access to the medicine will be restricted, patients will be denied valuable health benefits, and valuable resources may be wasted (e.g. GP consultations). The same applies up-scheduling, dependent on whether it is cost-effective and whether it is up-scheduled.

Many parameters have a natural minimum or maximum value (e.g. 0% probability or nil impact on health), or there is some (although it may be minimal) pre-existing evidence regarding the value of a parameter, or experts may have some idea of the plausible range of parameter values. If the scheduling decision remains unchanged regardless of the parameter value being at its maximum plausible range, then the scheduling decision made on the basis of the currently available evidence is likely to be appropriate regardless of the presence of uncertainty. On the other hand, a non-negligible risk that the scheduling decision may be inappropriate suggests that either the schedule of the medicine should not be changed or there may be some value in collecting further evidence.

Consequently, comprehensive sensitivity analysis will be key to conducting economic evaluations of down-scheduling decisions.

## 2.7.2. Methods to measure uncertainty

There are two different types of sensitivity analyses – deterministic and probabilistic.

Deterministic sensitivity analysis includes univariate, multivariate, threshold, scenario, and sub-group analysis:

- Univariate sensitivity analysis involves varying parameter values manually to test the sensitivity of the model's results to a specific parameter, while multivariate sensitivity analysis involves varying sets of parameters.[14] Lower and upper 95% confidence intervals should be applied when conducting univariate or multivariate sensitivity analysis. Arbitrary analyses, such as +/- 10% are not recommended.[14] Generally if varying the parameter values does not alter the ICER such that the funding decision changes, then the results are considered 'robust'. Univariate and multivariate sensitivity analysis enables decision makers assess the importance of a certain parameter and whether further research is required.
- Threshold analysis involves varying a parameter value until a certain ICER is reached. For example, the proportion of patients experiencing a rare adverse event could be varied until down-scheduling/up-scheduling would no longer be considered cost-effective. The threshold parameter value can then be presented to experts, who can indicate whether the value is plausible and thus whether down-scheduling/up-scheduling is unlikely to be cost-effective. This approach is most useful when there is limited evidence to inform parameter values.
- Scenario analysis involves varying one or more parameter values to some pre-specified amount (e.g. extreme values) or enabling or disabling parts of an economic model. Generally, if varying the parameter values does not alter the ICER such that the funding decision changes, then the results are considered 'robust'. Scenario analysis enables decision makers assess the importance of a certain parameter and whether further research is required. It can also be used to assess the impact of different regulatory decisions on health outcomes and healthcare resource use, such as the impact of requiring patients to complete a patient-screening questionnaire, or requiring patients to first be diagnosed by a medical practitioner.
- Sub-group analysis involves varying one or more parameter values to reflect the impact of scheduling decisions on health outcomes and resource use if only a sub-group of patients were only able to access the medicine OTC. For example, the screening tool used by pharmacists to assess whether patients can purchase sildenafil for erectile dysfunction through the pharmacist in New Zealand includes a restriction that the patient must be aged 35-70 years.[32]

Deterministic sensitivity analyses do not reflect how likely it is that the true parameter value will be a certain value. In probabilistic sensitivity analysis (PSA) (preferably) all parameters are varied simultaneously, with multiple sets of parameter values being sampled from a priori–defined probability distributions. The purpose of PSA is to estimate the uncertainty around the ICER, and thus the probability that re-scheduling a medicine is cost-effective. Guidelines are available regarding how PSA should be conducted.[11, 14]

PSA is typically conducted using Monte Carlo simulation methods. Parameter uncertainty is characterised using prior distributions.[11] Distributions may be non-parametric and based on patient-level clinical trials or observational data, or may be assumed parametric distributions with the shape and scale parameters (alpha and beta) obtained from the literature (e.g. based on reported means and standard errors). A potential value for each parameter ($\theta$) is bootstrapped from the associated distribution. Using the new set of values as inputs into the model, the ICER is then re-calculated. This process is repeated many times until the estimated average ICER becomes stable. Thus the uncertainty surrounding the ICER is characterised. Figure 2-6 illustrates the above process.

Table 2-13 presents the most plausible parametric distributions that can be used to characterise uncertainty. When identifying the appropriate data sources used to inform each parameter value, both the mean and standard error need to be extracted in order to conduct PSA. There are commonly adopted statistical standards that can be used to estimate the mean and standard error.[11]

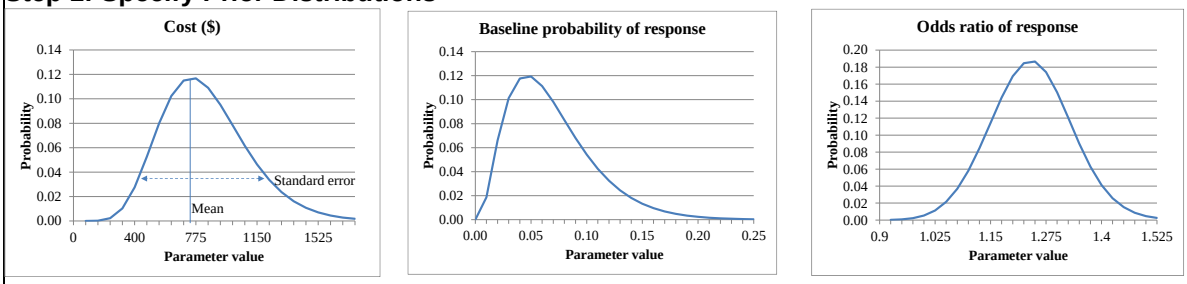
Where limited information is available about a parameter, a conservative approach should be adopted where the absence of evidence is reflected by a broad range of possible estimates.[14] For example, where the mean is known but not the 95% confidence intervals or standard errors, it can be assumed that the standard error was equal to half the mean;[133] and where the mean and standard error is not known non-informative priors should be used.

The results of PSA can be presented as a scatter plot on the cost-effectiveness plane or, preferably, as a cost-effectiveness acceptability curve (CEAC). The CEAC summarises the proportion of simulations that fall below a given threshold, which can be interpreted as the probability that down-scheduling is cost-effective.

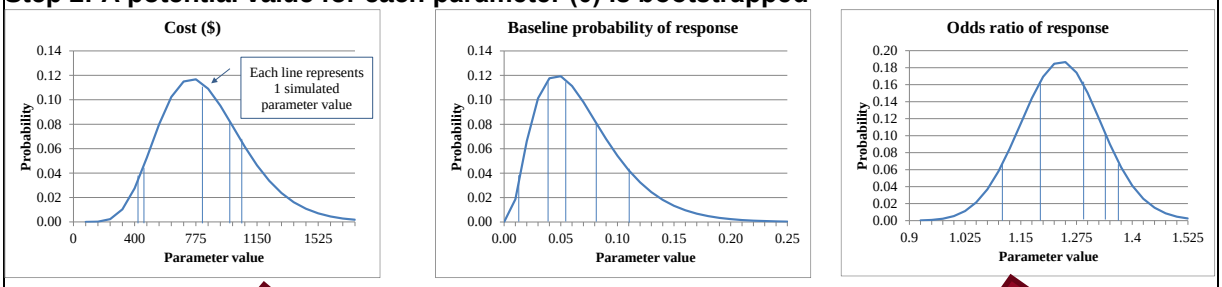
The probability that re-scheduling a medicine is cost-effective cannot be interpreted in the same way as per the traditional rules of inference.[11, 134] If traditional rules of inference were applied then the results would not be considered statistically significant if the probability of re-scheduling a medicine being cost-effective was less than 90% or 95%. But in this case, the expected net benefit of re-scheduling a medicine will be forgone if it is not implemented. Instead, down-scheduling is justified on health economic grounds if it has a greater than 50% probability of being cost-effective.

**Figure 2-6: Probabilistic sensitivity analysis**

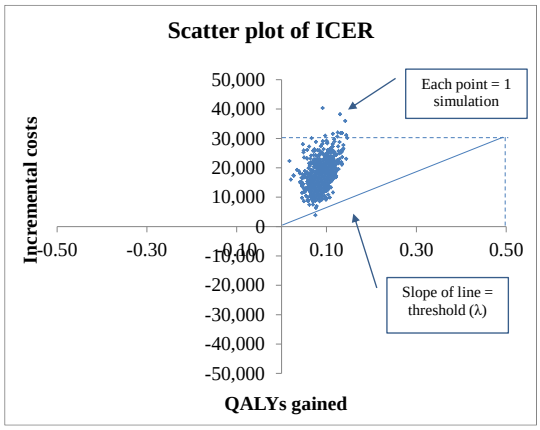
**Step 1: Specify Prior Distributions**




**Step 2: A potential value for each parameter (θ) is bootstrapped**




**Step 3: Using the new set of values as inputs into the model, the ICER is then re-calculated. Repeat ~10,000 times.**




**Step 4: Calculate the number of simulations under each $/QALY gained threshold (λ)**

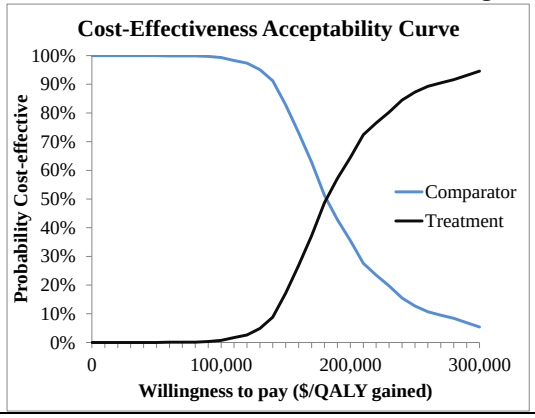


**Table 2-13: Parametric distributions used for probabilistic sensitivity analysis**

| Type of parameter | Distribution | Alpha | Beta |
|---|---|---|---|
| Probabilities with more than one outcome (e.g. response to treatment, stable disease, or non-response to treatment) | Dirichlet | The number of patients (n) experiencing each outcome | |
| Dichotomous probabilities (yes/no) | Beta | $\frac{mean^2 \times (1 - mean)}{SE^2} - mean$ | $alpha \times \frac{(1 - mean)}{mean}$ |
| ORs and hazard rate ratios | Log-normal | $\ln(mean)$ | $SE(\ln(mean))$ |
| Duration and resource use parameters (e.g. time between specialists consultations) | Gamma | $\frac{mean^2}{SE^2}$ | $\frac{SE^2}{mean}$ |
| Utilities | 1 – gamma | | |
| Disutilities | -gamma | | |

OR: odds ratio; SE: standard error.
Source: [11]

# 2.8. Interpreting results

In the context of scheduling decisions, there is likely to be both positive and negative impacts on health outcomes, and thus costs (see Figure 2-7).

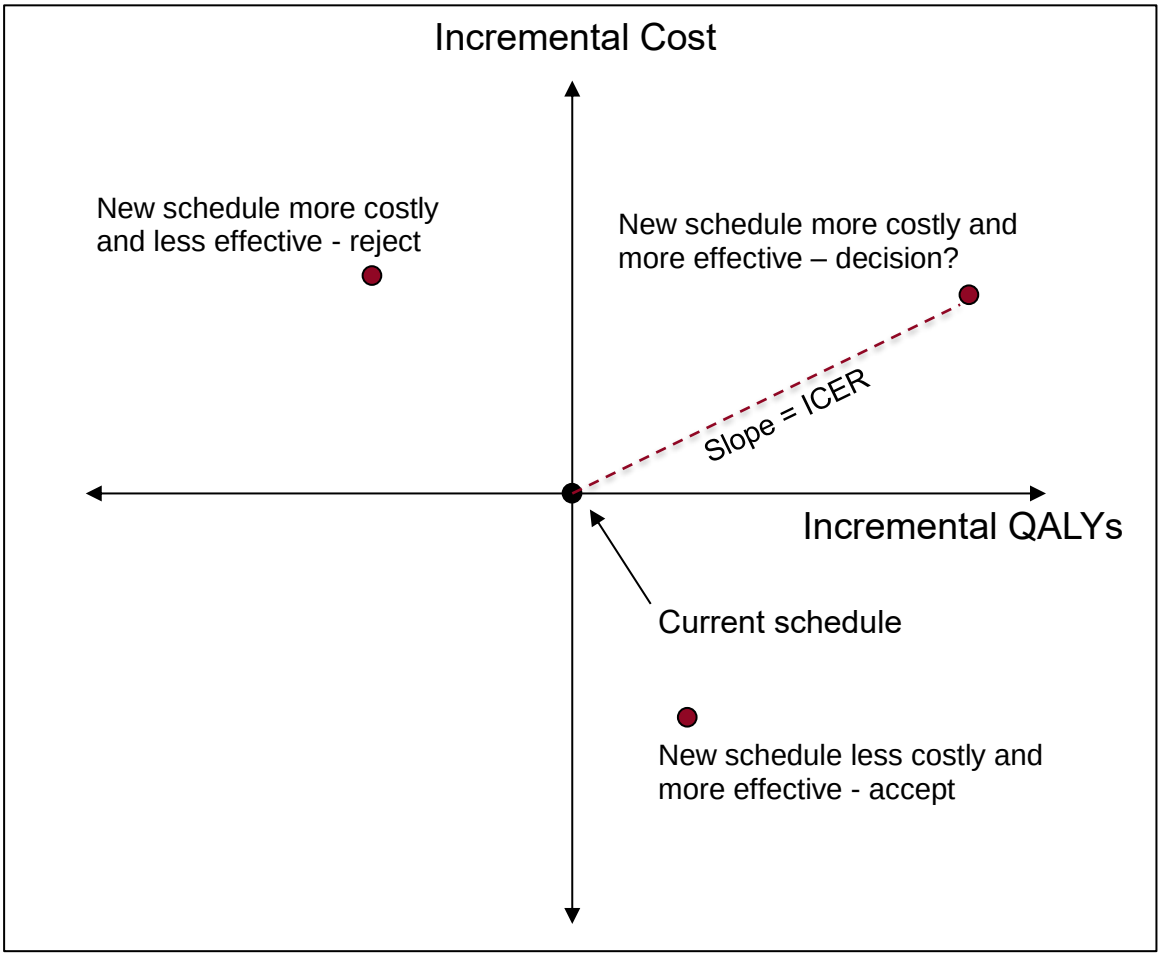
Focusing only on the net impact on costs may result in suboptimal decisions. If it expected that re-scheduling a medicine results in improved health outcomes and lowers costs, then there is strong support for the schedule change.

But what if re-scheduling a medicine results in improved health outcomes and increases costs? In this case, decision makers can compare the ICER to an implicit or explicit threshold, which represents the amount decision makers would be willing to pay for an additional health outcome. If the ICER is less than the threshold, then the intervention is considered value for money (or is 'cost-effective').[10] Thus there are situations where re-scheduling a medicine is optimum even if it increases costs.

In practice, decision makers rarely have a hard threshold, rather the amount they are willing to pay for an additional health outcome may increase or decrease due to a range of other factors.[135] As a result, we recommend simply presenting the results of the economic evaluation in a table format, which includes health outcomes and costs if the medicine remains at the current schedule compared to changes schedules, and the ICER associated with each health outcome (e.g. cost per QALY gained). We also recommend not drawing a conclusion regarding whether re-scheduling a medicine is cost-effective, and leaving this to the decision makers.

Note that applying an explicit threshold on behalf of the decision maker is effectively the same thing as applying a value of a statistical life year and estimating the net benefit, as per cost-benefit analysis.

**Figure 2-7: Incremental cost-effectiveness plane**




# 2.9. Summary

This section outlined an economic evaluation framework that could be used by sponsors and decision makers to inform decisions regarding whether a medicine should be listed on Schedule 4 (prescription only) or Schedule 3 (Pharmacist Only). While this section focuses on an economic evaluation framework to inform scheduling decisions in Australia, the approach can be adapted to other countries.

The use of an economic evaluation framework will ensure consistency across submissions for re-scheduling medicines considered by decision makers.

The economic framework is based on various guidelines currently available regarding how to conduct health economic evaluations, however with some adjustment to focus it towards informing scheduling decisions. While the framework outlines the preferred approach, it should not be considered to be prescriptive. Alternative approaches may be used depending on the condition and treatment, however the reasons for using an alternative approach should be clearly justified to ensure transparency.

An economic evaluation approach has several advantages, including: the use of economic modelling to synthesise evidence from a variety of sources; the aggregation of the impact of a wide range of different

health outcomes into a single measure (QALYs); and the consideration of the impact on healthcare resource use and costs.

The framework recognises the importance of avoiding making an inappropriate scheduling decision. However, it also recognises that the presence of uncertainty in the evidence is not the same as uncertainty in the scheduling decision. Reflecting the need to understand the sources of uncertainty and estimate the probability that re-scheduling a medicine is cost-effective, the framework recommends a suite of sensitivity analyses to be conducted. This enables decision makers to assess how important a certain parameter is and whether a down-scheduling decision should be delayed until further research is conducted. Scenario analysis can also be used to explore the impact of different regulatory scenarios.

This is not the first study to recommend an economic evaluation approach. In particular, Cohen et al (2013) published a paper outlining guidelines for assessing the economic impact of down-scheduling.[136] There are several limitations with these guidelines.

First, the authors recognised the need to consider patients switching from other prescription medicines or OTC medicines. However, the authors failed to consider patients with different conditions using the recently down-scheduled medicine.

Second, the authors also recognised the need to use economic modelling to synthesise all relevant evidence from a variety of sources. However, the authors did not recognise the importance for the time horizon, which should be long enough to capture all relevant costs and consequences, and is dependent upon the duration of adverse events, as well as the condition that the medicine aims to treat or prevent. The authors also do not mention discounting.

Third, the authors note that it is important to take into account clinical states and adverse events, but do not discuss the valuable role of estimating QALYs.

Fourth, the authors recommend a societal perspective is taken and discuss the inclusion of work productivity-related costs, but did not discuss the potential for double counting and the equity implications.

Fifth, the authors provided limited discussion regarding the role of uncertainty analysis and the insights it can generate.

Finally, the authors provide sparse detail about how to estimate each parameter and the potential biases of the different approaches that may be used.

In comparison to Cohen et al (2013), the economic evaluation approach presented in this report is more comprehensive in terms of the scenarios considered and the methods discussed.

# 3. Case study: down-scheduling triptans

Removed due to copyright restrictions.

Available at: Parkinson, B. Gumbie, M., Cutler, H., Gauld, N., Mumford, V., Haywood, P. Cost-effectiveness of reclassifying triptans in Australia: application of an economic evaluation approach to regulatory decisions. Value in Health (EPub ahead of print). 10.1016/j.jval.2018.09.2840

# 4. Case study: Down-scheduling the oral contraceptive pill

Removed due to copyright restrictions.

Currently submitted: Gumbie, M., Parkinson, B., Cutler, H. Gauld, N., Mumford, V. Is Reclassification of the Oral Contraceptive Pill from Prescription to Pharmacist-Only Cost-Effective? Application of an Economic Evaluation Approach to Regulatory Decisions

# 5. Discussion and conclusion

This report presented an economic evaluation framework to help inform scheduling decisions regarding whether a medicine should be available via prescription only (Schedule 4 in Australia) or Pharmacist Only (Schedule 3 in Australia). The practical application of the economic framework was demonstrated using two Australian case studies: down-scheduling triptans and down-scheduling OCPs. These case studies illustrated the advantages of an economic evaluation approach, but also some inherent limitations.

## 5.1. Policy implications

The case studies illustrated the advantages to applying an economic evaluation approach to inform scheduling decisions.

First, the two case studies demonstrated that an economic evaluation approach can improve the consistency in the type of evidence considered when making scheduling decisions.

Second, economic modelling was applied in both case studies, one being a decision tree with a time horizon of ten years and the other being a Markov model with a time horizon of 35 years. Thus the case studies demonstrated that economic modelling can be used to synthesise data from a variety of sources, and predict the overall impact of a scheduling decision on health outcomes and resource use before it occurs.

Third, a wide range of health outcomes were aggregated into QALYs in both case studies. In the triptans case study the impact on the duration of migraines were combined with common adverse events, such as dizziness, less common cardiovascular and gastrointestinal adverse events, and rare adverse events, such as serotonin syndrome. In the OCP case study the impact on pregnancies were combined with the risk of STIs, adverse events, such as depression and cardiovascular adverse events, and ovarian cancer.

Fourth, the impact on healthcare resource use and costs from re-scheduling a medicine were included in both case studies. Healthcare resources are both valuable and scarce. Their use generates an opportunity cost because they could be used to treat other patients or reduce waiting lists.

Fifth, the value of the ICER to inform the appropriate scheduling decision was demonstrated in the triptans case study. It was not required in the OCP case study as down-scheduling was predicted to improve health outcomes and be cost-saving.

Finally, sensitivity analyses on the economic models enabled the assessment of the importance of each parameter and whether the down-scheduling decision should be delayed until further research is conducted. For example, the triptans case study found that the risk of serotonin syndrome had little impact on the results and further research was not required. Sensitivity analysis avoids the risk of placing too much or too little importance on risks or benefits where the clinical impacts or the frequency are “unknown” due to limited data.

Sensitivity analyses on the economic models also enabled the assessment of different regulatory scenarios, including the impact of patient-screening questionnaires and whether only a sub-group of patients should be able to access a medicine directly through pharmacists. For example, the OCP case study illustrated that the TGA may wish to consider restricting access to Pharmacist Only OCPs to younger women.

The case studies also illustrated that undertaking an economic evaluation on scheduling decisions can provide decision makers with new insights that they may not have been aware of otherwise.

Both case studies found that results were not sensitive to some uncertain parameters the TGA was concerned about when rejecting the down-scheduling applications, such as the risk of serotonin syndrome with triptans. On the other hand, both case studies identified other uncertain parameters had a significant impact on the results that did not appear to be considered by the TGA, such as the risk of pregnancy in women not using contraception and not trying to conceive.

Both case studies found that the proportion of patients switching from obtaining the medicine by prescription to obtaining the medicine OTC had a minor impact on the results. This is because these patients are already being treated with the medicine. While benefits for these patients include reducing time to symptom relief, improving adherence and reducing GP consultations, these benefits are low relative to the benefits of improving the access to treatment by patients not currently treated or using other treatments.

Reflecting this nuance, both case studies identified that the efficacy and safety characteristics of other treatments (pharmacological and non-pharmacological treatments) is also important to consider when deciding on the proposed medicine to be re-scheduled.

## 5.2. Limitations

There are several limitations with using an economic evaluation approach to help inform scheduling decisions that policy makers should consider before implementation.

The approach is dependent on the availability of a wide range of good-quality evidence. This is more likely with medicines that have been available for a long period of time, enabling the collection of post-market data on patient behaviour and adverse events.

The approach is also condition dependent. The complexity of modelling and the need for evidence increases exponentially with the number of conditions that the medicine can treat.

The complexity of modelling also increases exponentially in complexity when up-scheduling and down-scheduling decisions overlap, as in the case of triptans and codeine. A delay is needed between down-scheduling decisions to understand changes in patient behaviour.

Finally, the two case studies were limited by the availability of evidence regarding how individuals will respond to the re-scheduling decision, for both patients with and without the condition included in the medicine's indications. The case studies were reliant on survey data, which may suffer from different potential sources of bias. In theory, discrete choice experiments can be used to predict the impact of scheduling changes and there is some evidence that discrete choice experiments are able to predict choices within sample[89-91] and out of sample.[80, 92-95] However further research is required to demonstrate the applicability of this method to re-scheduling decisions, and the accuracy of discrete choice experiments relative to survey methods.

## 5.3. Where to from here?

The results of any economic evaluation should not be considered in isolation, but as part of the broader body of evidence regarding the types of health impacts, the extent of the available evidence, who will be affected, and the role of medical practitioners and pharmacists in mitigating any risks.

If decision makers wish to place different weights on the different health outcomes and costs decision makers can incorporate the detailed results from the economic evaluation into a MCA, as per the Brass framework.[9] Appendix 1 presents example of this using the triptans case study.

The economic evaluation framework presented in this report is not a final version. Any change in the scheduling regulation needs to be driven by the TGA following extensive consultation with the committee members, State governments, medical practitioners, pharmacists, patients, health researchers and health economists.

Ultimately this report aims to start a conversation and encourage decision makers to consider a more innovative approach to down-scheduling decisions, and potentially maximising the health of Australians.

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# Appendix 1

**Example application of the Brass approach to triptans**

| | Frequency of behaviour | Clinical Impact | Overall score | Post marketing issues / plan |
|---|---|---|---|---|
| **Benefit attributes** | | | | |
| Shortened time to treatment | 1 | 1^ | 1 | |
| Reduced use of less effective or less safe alternatives non-pharmacological treatments or OTC medicines | 2 | 2* | 4 | |
| Shortened time to symptom relief | 3 | 3** | 9 | |
| Decreased GP consultations | 2 | 1# | 2 | |
| Decreased healthcare costs from improved clinical outcomes | 2 | 2## | 4 | |
| **Risk attributes** | | | | |
| Increased adverse events | 1 | 3 | 3 | More research is required on the risk of cardiovascular events with triptans |
| Increased risk of interactions between medicines | 1 | 1 | 1 | While the risk and impact of serotonin is uncertain, it is unlikely to affect the results. |
| Incorrect diagnosis and leakage to other indications | 1 | 1 | 1 | More research is required on the use of triptans by non-migraineurs |
| Increased risk of over dosing due to inadequate efficacy or a belief that OTC medicines are less effective | 2 | 2 | 4 | More research is required on the risk of chronic headache with triptans |
| Increased medicine costs due to leakage to other indications | 3 | 3^^ | 3 | |
| Increased healthcare costs due to more frequent or severe adverse events | 1 | 2## | 2 | |
| Increased pharmacist time counselling patient | 1 | 1 | 1 | |

^ A low score was given to avoid double counting with time to symptom relief.
* Given a 2 as the second largest contributor to QALYs gained was reduced gastrointestinal adverse events.
** Given a 3 as QALYs gained were mainly due to reduced duration of migraines.
# Given a 1 as total costs were not significantly driven by GP costs.
## Given a 2 as the second and third largest contributors to costs were common adverse events and gastrointestinal events.
^^ Given a 3 as total costs were mainly due to increased medicine costs.
Source: Adapted from Brass (2013)[62]