

Rethinking medicines decision-making in Australian Hospitals

Guiding Principles for the
quality use of off-label medicines

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Council of Australian Therapeutic Advisory Groups

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Executive Summary

The purpose of these Guiding Principles is to provide a framework to support the quality use of off-label medicines in Australian public hospitals. These principles are intended to assist decision-making by health professionals, consumers and Drug and Therapeutics Committees in the evaluation, approval and use of these medicines.

The term 'off-label' is applied when a medicine is used in ways other than specified in the Australian Therapeutic Goods Administration (TGA) approved product information, including when the medicine is prescribed or administered:

- for another indication
- at a different dose
- via an alternate route of administration
- for a patient of an age or gender outside the registered use.

The clinical, safety, ethical, legal and financial issues related to the off-label use of medicines, require a careful and responsible approach to ensure delivery of quality use of medicines (QUM) to the Australian public. These Guiding Principles seek to support QUM and to minimise unintended harm by providing a framework for decision-making.

In general, off-label use of a medicine should only be considered when the TGA approved use of a registered medicine does not address the clinical needs of patients.

In determining the appropriateness of using a medicine off-label, there should be sufficient evidence to support its efficacious and safe use, and an overall favourable harm: benefit ratio for the intended clinical use and population.

These Guiding Principles are a guide for the decision-making process, based on a systematic evaluation of the evidence of harm and benefit of the proposed use. The following four categories of off-label use depend on the level of supporting evidence and clinical circumstances:

- routine use
- exceptional/individual use
- conditional use, with evidence development
- research or investigational use.

Use is not recommended, when a proposed off-label use does not fall into one of these four categories.

Recommendations for institutional approval, informed consent, outcome evaluation and monitoring are provided for each category.

THE OVERARCHING GUIDING PRINCIPLES ARE:

1. Consider the off-label use of a medicine only when all other options, including the use of medicines approved by the TGA, are unavailable, exhausted, not tolerated or unsuitable.

2. Use high-quality evidence to determine appropriateness of off-label medicine use.

3. Involve the patient/carer in shared decision-making when recommending the use of an off-label medicine.

4. Consult the Drug and Therapeutics Committee when prescribing an off-label medicine, except when the use of a medicine off-label is considered routine.

5. Ensure appropriate information is available at all steps of the medicines management pathway.

6. Monitor outcomes, effectiveness and adverse events.

7. Consider liability and accountability when using medicines off-label.

Overview

Purpose

The purpose of these Guiding Principles is to provide a framework to support the quality use* of off-label medicines in Australian public hospitals. These principles seek to assist decision-making by health professionals, consumers and Drug and Therapeutics Committees (DTCs) in the evaluation, approval and use of these medicines.

Background

For a medicine to be marketed in Australia, it must have approval from the Therapeutic Goods Administration (TGA). This is to ensure that the medicine meets Australian standards for quality, safety and effectiveness. The process is initiated by the sponsor, who applies to the TGA for approval of a medicine with indications, doses and routes of administration nominated by the sponsor.¹ The TGA evaluates the information available, taking into account whether the safety, quality and efficacy of the medicine is established satisfactorily for the purposes for which it is to be used. Approval will be for specific indications (population and disease), doses and routes of administration. All elements of the TGA's decision are reflected in the product information (PI) (also approved by the TGA) and in the entry for the medicine in the Australian Register of Therapeutic Goods (ARTG).

The indications for which the sponsor seeks TGA approval may be influenced by other factors, such as commercial considerations of the sponsor, i.e. the TGA approved medicine may not reflect the full range of indications for which there may be evidence that the medicine could effectively and safely be used.^{2,3} Also, the indications approved by the TGA may not be as extensive as those sought by the sponsor in the application.

The sponsor pays all the costs of this process, which also includes the cost of evaluation by independent experts appointed by the TGA. These costs may serve as a disincentive for the sponsor to seek TGA approval or update the PI when new information becomes available, especially for medicines or uses with a small market (e.g. rare diseases) or for 'off patent' medicines.

Once approved for marketing in Australia, the process does not preclude the medicine being used off-label, i.e. for indications, doses or routes other than those specified in the TGA approved PI.⁴ Lack of TGA approval of a medicine does not imply that a drug is ineffective, contraindicated or disapproved. It may mean that it is not economically viable for the sponsor to seek approval (despite good evidence to support use). It may also mean that there is insufficient evidence for approval or the effectiveness and safety of the medicine in a particular situation has not been examined.⁴⁻⁶ Furthermore, there may be ambiguity around whether a medicine is approved in a

certain setting and would be considered off-label. This is complicated by a lack of clarity in the language used in the approved PI, particularly for older medicines.

Off-label use of medicines is a common therapeutic strategy for many clinicians and patients in Australia, especially in specialised care settings. In some circumstances, off-label use of a medicine may represent the best available option for a patient or the standard of care.⁷ The off-label use of medicines allows patients to access innovative and potentially useful new medicines or older medicines for new indications, doses or routes based on recent evidence.⁸ In patient groups, such as paediatrics, oncology, psychiatry and palliative care, off-label use of medicines is prevalent⁹ and may provide the only treatment option.⁸

The widespread nature of off-label prescribing in the paediatric population is well documented; more than 40-90% of hospitalised paediatric patients worldwide receive at least one unapproved medicine.¹⁰ The underlying reasons for this situation are complex, with important consequences, including potentially suboptimal QUM. Recent evidence suggests that such use can be associated with increased incidence and seriousness of adverse drug reactions.¹⁰⁻¹³ Furthermore, some established and well accepted off-label uses have been shown to be ineffective or harmful when prospectively studied in the paediatric population.^{14,15} Major drug regulatory reforms in the US and the European Union are driving increased paediatric medicines research and improving the availability of evidence on the efficacy and safety of medicines in this population.¹⁶ This information is not always reflected in the Australian PI in a timely manner.¹⁷

In general, off-label medicines use has less supporting evidence and has undergone less scrutiny regarding efficacy, safety and cost-effectiveness than medicines used as per the TGA approved indications; the balance of benefit and harm associated with off-label medicines use is often less well known.¹⁸ Therefore, the off-label use of medicines may result in a lack of therapeutic benefit and/or patient harm, as less is known about its use in specific circumstances.^{14,19-22}

The ethical and legal issues associated with using a medicine off-label also need to be considered. Although off-label prescribing is not illegal in Australia and is not regulated by the TGA, it is an offence under the *Therapeutic Goods Act* for a sponsor to promote the use or supply a medicine for an indication that is not approved or to promote the supply of an unapproved medicine. Prescribers are expected to use their 'professional judgement' to determine appropriateness in individual patients, and may be exposed to greater potential medico-legal risk.²³ There is often limited information or guidance

* Quality Use of Medicines (QUM) means judicious selection of treatment options; appropriate choice of medicine when a medicine is required; and safe & effective use of medicines. The National Strategy for Quality Use of Medicines. Canberra: Department of Health and Ageing; 2002.

to inform their decisions, raising ethical issues pertaining to informed consent. For a patient to consent to take a medicine it is expected that they are provided appropriate information, in relation to the safety and effectiveness of the proposed treatment, available alternatives and associated risks, so that they can evaluate their options.²⁴ Currently, there is considerable variability in the level of awareness and knowledge about these issues among decision-makers²⁵⁻²⁷ and in approaches to how they are addressed.^{5,7}

There can also be financial implications associated with off-label medicines use. While some off-label prescribing involves expensive medicines there are further costs to the patient and the health system in terms of uncertain efficacy and toxicity.¹⁸ Furthermore, prescribing a medicine off-label can have financial implications in the ongoing supply for the patient. The Pharmaceutical Benefits Scheme (PBS) Schedule lists the medicines available to patients at a price subsidised by the government. Currently, the PBS only subsidises medicines on an approved list limited to specific indications or patient groups as approved by the TGA. Therefore, prescribing medicines off-label requires an understanding and agreement between the patient and the prescriber as to how the medicine will continue to be obtained. Options may include access via a private prescription for which the patient covers the cost or the prescriber may seek approval from a hospital DTC to fund the ongoing supply. This has implications for the cost of treatment and access, if the patient is required to return to the hospital for prescriptions and supply on a regular basis.

The clinical, safety, ethical, legal and financial/cost issues related to off-label use of medicines require a careful and responsible approach to ensure delivery of QUM to the Australian public.⁵ These Guiding Principles seek to support QUM and to minimise unintended harm by providing a consistent framework for decision-making.

Context

Developing a national approach to address the quality use of off-label medicines was supported by the National Medicines Policy Executive in 2010. A report to the Australian Health Ministers Advisory Council in 2005 by the Paediatric Pharmaceuticals Working Group had also recommended developing national guidance on this issue.

The NSW Therapeutic Advisory Group (NSW TAG) has developed a consensus framework for assessing appropriateness of off-label medicines use, with a focus on rigorous evidence review.⁵ This framework forms part of the NSW Health Policy²⁸; is incorporated into policy by various state²⁹ and national organisations and professional bodies.³⁰ Similar approaches have also been described internationally in recent years.³¹⁻³⁶

These Guiding Principles were developed by building on concepts and themes from previous key work on off-label medicines use and followed a systematic process of multidisciplinary expert review and national consensus development, coordinated by CATAG (see Appendix 1). These Guiding Principles represent the initial phase of an evolving process, which will include broader stakeholder engagement and future work to support optimal use and implementation of the Guiding Principles in a range of settings (see Appendix 2).

Definition

For the purposes of these Guiding Principles the term 'off-label' use applies when the medicine is used in ways other than specified in the TGA approved product information including when the medicine is prescribed or administered:

- for another indication
- at a different dose
- via an alternate route of administration
- for a patient of an age or gender outside the registered use.

This definition excludes:

- an unlicensed medicine that is yet to be evaluated or approved in Australia by the TGA
- TGA registered medicines whose formulation is modified (e.g. extemporaneous or compounded preparations, such as preparation of special creams or a liquid suspension by crushing tablets). This is considered unlicensed use.

Scope

These Guiding Principles are designed to guide DTCs, prescribers and consumers in public hospitals in their decision-making about off-label medicines use. Medicines use for patients in public hospitals includes the inpatient, discharge, outpatient and continuity of care issues.

In general, these Guiding Principles are applicable to both off-label and unlicensed uses, but there are additional considerations relevant to unlicensed and extemporaneous medicines, such as evaluation of the quality and stability of the product, appropriateness of changes in route and other legal issues that have not been addressed.

These Guiding Principles are relevant to community or private hospital settings. However, further consultation is required to investigate their applicability in these settings.

GUIDING PRINCIPLES

The purpose of these Guiding Principles is to provide a framework to support decision-making for the evaluation, approval and use of off-label medicines

In determining the appropriateness of using a medicine off-label, there should be sufficient evidence to support its efficacious and safe use, and an overall favourable harm : benefit ratio for the intended clinical use and population. An overall guide for the decision-making process and associated recommendations for institutional approval, informed consent, outcome evaluation and monitoring, depending on the level of evidence supporting such use is provided in Figure 1.

Prescribing a medicine off-label is generally considered when there is no TGA approved medicine for the patient and the condition; if new information about a medicine becomes available that is not reflected in the PI or when standard or alternative therapy has been tried and failed. This acknowledges that in some populations there may be limited TGA approved treatment options.

When considering the use of a medicine off-label, there should be a well justified clinical need, biological or pharmacological plausibility and/or other information supporting the proposed use. An in-depth discussion

with the patient/carer about potential benefits and risks is necessary when making the decision to use a medicine off-label. This is particularly important when the use of a medicine off-label is being considered on the wishes of the patient/carer. In general, the off-label use of a medicine should only be considered when the approved use of a registered medicine does not address the clinical needs of patients.²⁸

These Guiding Principles are intended to assist decision-making by health professionals, consumers and DTCs in their evaluation, approval and use of these medicines.

FIGURE 1: Assessing appropriateness of off-label medicine use and process for approval, consent and monitoring

Gazarian M, Kelly M, et al. Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust 2006; 185(10):544-548.
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a See Guiding Principle 2 and Appendix 3 for detailed guidance in answering this question
b See Guiding Principle 2, point 5 for description of criteria for this category

c See Guiding Principle 4
d See Guiding Principle 3
e See Guiding Principle 6

Drug and Therapeutics Committee
***** Human Research Ethics Committee

GUIDING PRINCIPLE 1

Consider the off-label use of a medicine only when all other options, including medicines approved by the TGA, are unavailable, exhausted, not tolerated or unsuitable.

Prior to considering using a medicine off-label, a TGA approved medicine or other treatment options should be

considered. If the available treatment options, including TGA approved medicines have been exhausted, or are not tolerated or unsuitable for the patient then using an off-label medicine may be considered. This acknowledges that in some populations there may be limited TGA approved treatment options. In some situations, off-label medicine use may be common place and may be the only treatment option available and represent best therapy.

Prior to considering an off-label medicine there needs to be a well justified clinical need, biological or pharmacological plausibility and other information supporting the proposed use (see Guiding Principle 2).

GUIDING PRINCIPLE 2

Use high-quality evidence to determine appropriateness of off-label medicine use.

1. The first step in evaluating the appropriateness of proposed off-label use of a medicine should focus on answering the question, 'Is there high quality evidence supporting this medicine's use in such a manner?'

This decision should be informed by a critical evaluation of high-quality 'patient-based research evidence about clinical effectiveness and safety'¹⁰ derived from studies conducted in the relevant population and for the intended use. These decisions should be primarily informed by high-quality research evidence, particularly for newly marketed medicines (or proposed new uses of older medicines).⁵ The types of high-quality research evidence needed for evaluating new medicines proposed for use in the paediatric population have been previously described and these principles can be generalised to other populations (see Appendix 3).

Accepted guidelines for critical appraisal of therapeutic studies,³⁷⁻⁴⁰ for grading of strength of evidence^{41,42} and for deciding about applicability of research evidence to individual patient circumstances^{43,44} can be used.⁵ Other critical appraisal guidelines and evidence grading schema may also be used.

Additional key points:

- A. Particular considerations apply for evidence evaluation in *special populations*, including paediatric and geriatric patients.
- B. The available evidence should be weighed against the clinical *seriousness* of the underlying condition. As a general rule, the less serious the health need, the higher the level of evidence needed to support such use.
- C. If an off-label use is likely to be routine and widespread, additional information about *cost-effectiveness* is needed for the relevant context in which use will occur.

2. In some instances, high-quality research evidence supporting the off-label use of a medicine may not be available and may be unlikely to ever become available. Recommendations from authoritative sources (e.g. medicines compendia, professional societies) that are supported by limited evidence and consensus opinion (based on extensive experience) may be appropriate to consider for established uses of older medicines. However, this type of evidence is generally considered to be of lower quality and should not be used to support routine off-label uses for newly marketed medicines (marketed for less than 3-5 years) or proposed new uses of older medicines.
3. If therapeutic alternatives are available to treat a particular condition, evidence about *comparative* clinical effectiveness, safety and cost-effectiveness between the off-label medicine and TGA-approved alternatives should be sought. The medicine with a *demonstrated advantage* in clinical effectiveness and/or safety and/or cost-effectiveness (in the relevant population and for the intended use) should be chosen.¹⁰

Additional key points:

- A. Comparisons of the safety of a newly marketed medicine proposed for off-label use versus an older medicine are often unfairly skewed in favour of the newer medicine, due to the limited safety data available at the time of marketing. This should be borne in mind when evaluating comparative data.
- B. The safety profile of medicines can be variable in different populations e.g. paediatric vs. adult patients. Therefore, safety data derived from the relevant population should optimally inform these evaluations.

4. *Independent expert judgements* will be needed to inform decisions about the type of evidence appropriate for a given health issue or context, to evaluate its validity, as well as interpret its clinical meaningfulness and decide on its applicability.

Additional key points:

- A.** Health professionals with a combination of expertise, including relevant *clinical, therapeutics* and *evidence evaluation* expertise, should be involved in making these judgements.
- B.** Decisions about off-label uses in specific populations should involve health professionals with specialised clinical and therapeutics expertise in the relevant area(s).

5. The overall recommendation, based on evaluation of the evidence for the proposed off-label use of a medicine may be in one of four categories or not recommended, described below.

CATEGORY	Example*
ROUTINE USE Where there is 'high' quality evidence supporting the safe, efficacious and cost-effective use of the medicine off-label and an overall favourable harm : benefit ratio for the intended clinical use and population.	<ul style="list-style-type: none"> Once daily dosing of gentamicin (adults and children) Valproate for migraine (adults) Morphine for dyspnoea in palliative care (adults) Rituximab for rheumatoid arthritis (adults)
EXCEPTIONAL/INDIVIDUAL USE Where there is 'low' or 'very low' quality evidence, but potential benefits appear greater than potential harms, based on available evidence, in individual clinical circumstances where pre-specified criteria are met, e.g. serious or rare condition and no alternative treatments are available, or have been exhausted.	<ul style="list-style-type: none"> Topiramate for severe cluster headaches in an adult unresponsive to standard therapy and is unable to work due to headaches Rituximab for chronic, refractory immune thrombocytopenic purpura (adults)
CONDITIONAL USE, WITH EVIDENCE DEVELOPMENT Where there is 'low' to 'moderate' quality evidence, but potential benefits appear greater than potential harms and there is reasonable justification for use in certain types of patients. The relevant group of patients should be defined by pre-specified criteria (e.g. disease type and severity, age, standard treatments that have been tried and failed) and receive treatment according to an agreed protocol. The condition of such use should involve systematic reporting of effectiveness and safety outcomes so that an evidence base can be developed. Reviewing appropriateness of continued therapy at regular intervals (for the individual and group of patients) should occur.	<ul style="list-style-type: none"> Infliximab for moderate-severe Crohn's disease in children < 6 years of age, refractory to all standard therapy (TGA approval for children > 6 years of age with refractory disease. Longer term safety profile in children is unclear) Rituximab# in adults with systemic lupus erythematosus, with moderate-severe active disease, where pre-specified standard immunosuppressive therapy has failed
RESEARCH OR INVESTIGATIONAL USE If there is 'low' or 'very low' quality of evidence, with uncertain benefits and harms that are unknown or which may be significant, but where there is potential for clinical benefit then this is classified as investigational or experimental to be considered to be used via a research protocol and reviewed and approved by a Human Research Ethics Committee. ^{31,33}	<ul style="list-style-type: none"> Levetiracetam versus standard therapy for long-term treatment of seizures in children < 4 years of age (TGA approved for children > 4 years of age with partial onset seizures, as add-on therapy) Rituximab# in adults with systemic lupus erythematosus with moderate-severe active disease refractory to standard immunosuppressive therapy
NOT RECOMMENDED If there is a 'low' or 'very low' level of evidence with uncertain benefits or harms, or the available evidence indicates that the overall harm : benefit ratio is (or would be) unfavourable for the intended clinical use or population. ^{5,10}	<ul style="list-style-type: none"> Proton pump inhibitors (PPIs) in infants < 12 months of age with gastro-oesophageal reflux (GOR) (not TGA approved in this age group). Although PPIs are widely used in infants < 12 months to treat GOR, recent research evidence indicates PPIs are not effective in infants in this age group and longer term safety data are lacking⁴⁵, suggesting that the overall harm : benefit ratio may be unfavourable in this age group. Rituximab in adults with multiple sclerosis (available evidence indicates no benefit in this condition)

* Examples are provided to illustrate the categories and do not imply a treatment recommendation. They are current at the time of publication but their status may change over time with a constantly evolving evidence base.

Where the evidence base for a particular off-label use is equivocal or contentious (e.g. rituximab in SLE, where there is conflicting evidence from recent RCTs and previous open, uncontrolled observations), future off-label use could occur either as part of a formal "research" protocol, or as part of a DTC approved "treatment" protocol, within the "conditional use" category. The potential biases inherent in observational studies (e.g. tendency to overestimate treatment efficacy) apply to evaluation within the latter category. These should be carefully considered when choosing between the "research" vs. "conditional use" options for different health issues and contexts. In some cases, approved use for a particular medicine and indication may potentially occur in both categories concurrently.

GUIDING PRINCIPLE 3

Involve the patient/carer in shared decision-making when recommending an off-label medicine.

Informed consent should be obtained every time an intervention is offered to a patient, whether it is a surgical intervention or a medical intervention, such as the prescribing of a medicine. Considering the health literacy of the patient is an essential component of this process. In each situation it is expected that patients (including those from non-English speaking backgrounds and/or parents/carers) have received and understood information appropriate to their needs, in order to be able to evaluate their treatment options.⁴⁶

This information should optimally be provided in both written and verbal forms, and there should be an opportunity for discussion. The provision of an off-label medicine does not change this requirement. When a medicine is prescribed off-label, this should be made explicit, along with expansion of the associated uncertainties. Patients should be advised when there is a TGA approved alternative available and why the off-label use is being recommended. Discussion of financial cost implications and access issues is necessary and should occur prior to initiation of therapy.

In addition, the level and quality of evidence available to support the use of a medicine off-label plays a role in the decision about the nature and documentation of the informed consent process. This is described below and in Figure 1.

ROUTINE USE

When medicines are used off-label routinely and there is high-quality evidence supporting such use, it is appropriate to follow the usual process for consent to therapy, with provision of information and discussion. This should occur as part of usual clinical care and does not require additional measures.

In some cases, it may be appropriate to explain the reason for prescribing the medicine off-label and what this means.⁷ This will be a matter of clinical judgement, especially if there is something known about the patient that would indicate that they would attach some significance to this aspect. In this case, documentation of this discussion and consent in the medical record may be appropriate (in some cases, obtaining written informed consent may be judicious).

EXCEPTIONAL USE

When the use of the off-label medicine has low or poor levels of evidence and has received approval for use in a specific patient, written informed consent should be obtained, with documentation of the reasons for use in the medical records. In this case, there is usually more uncertainty about the benefits and harms with the use of the medicine. Detailed discussion about these aspects with the patient and/or carer, as well as the benefits/harms of available alternatives is required.

CONDITIONAL USE

When the off-label medicine has received approval for use according to pre-specified criteria, written informed consent should be obtained, with documentation of the reasons for use in the medical records. In this case, there is usually more uncertainty about the benefits and harms with the use of the medicine. Approval of use is conditional on further monitoring and assessment of effectiveness and safety. If these conditions are not met or if new information indicates an unfavourable harm : benefit profile, then the approval may be reviewed and there is potential for discontinuation of the medicine. Information collected about the use of this medicine may be shared with others in order to add to knowledge about this medicine. Detailed discussion about these aspects with the patient and/or carer, as well as the benefits/harms of available alternatives and consent to potentially sharing information with others, is required.

RESEARCH USE

It is necessary to explain to the patient that ethically to prescribe this medicine it is necessary to use it in a research manner. Requirements include: provision of written patient information; written informed consent, as part of an approved research protocol; and reporting of outcomes (with appropriate regard to privacy).

NPS MedicineWise provides a guide to the questions a patient should ask about their medicine at <http://www.nps.org.au/conditions-and-topics/topics/how-to-be-medicinewise/making-wise-choices-about-medicines/questions-to-ask-your-doctor>. This guide outlines the questions to ask about any medicine and includes information about:

- brand name and active ingredient
- how to take the medicine
- expected benefits of taking the medicine
- possible side effects of the medicine
- other treatment options.

It is recommended that general information regarding off-label use of medicines is also supplied.

Decisions by DTCs or ethics committees regarding the off-label use of medicines, along with the rationale for these decisions, should be communicated to the patient, especially when it is not approved. This communication should be carried out by an appropriate person (preferably a senior clinician), who can competently explain the complexities of the information in terms the patient or carer can understand.

Discussion of continuity of supply, care and medication management, and ongoing costs also need to occur with the patient. It is critical that this involves engagement of all of the patient's care providers (in the hospital, community and aged-care settings).

GUIDING PRINCIPLE 4

Consult the Drug and Therapeutics Committee when prescribing an off-label medicine, except when the use of a medicine off-label is considered routine.

Prescribers should always consider consulting the local/health network/state DTC to use a medicine off-label, except when the use of a medicine off-label is considered routine use (following application of Guiding Principles 1 and 2).

DTCs should have an approval process for the off-label use of medicines and be appropriately resourced for this function. (Refer to the CATAG document - *Achieving effective medicines governance: Guiding Principles for the roles and responsibilities of Drug and Therapeutics Committees in Australian public hospitals*. www.catag.org.au)

DTC consultation should always be sought and approval obtained for certain categories of proposed off-label uses. These categories include:

- a new medicine (been marketed for less than 3-5 years) as there is less knowledge of the medicine and its effects
- medicine to be used in a new (innovative or novel) way
- potential for serious adverse effects (if known)
- new medicines or proposed new uses in vulnerable populations (e.g. paediatrics, palliative care, elderly, pregnant, multiple morbidities)
- significant cost implications to patients and/or the institution.

Information regarding the decision made by the DTC (including any conditions and review requirements attached to the use of the medicine) should be recorded in the patient's permanent health record.

As per Guiding Principle 3, these decisions, along with the rationale should be communicated to the patient in a timely manner and by an appropriate person.

When the use of a medicine off-label is considered to be urgent and an individual patient request is made outside a normal meeting cycle of the DTC, then the DTC must ensure there is a process in place to facilitate rapid assessment according to these guiding principles.

GUIDING PRINCIPLE 5

Ensure appropriate information is available at all steps of the medicines management pathway.

When considering using a medicine off-label, it is important that all partners in the medicines management pathway at all levels of the health system, have appropriate information available, whether they are evaluating, prescribing, dispensing, administering or taking the prescribed medicine. They need to be able to make an informed decision regarding the appropriate use of the medicine off-label, to enable QUM.

The information available at each step of the medicines management pathway needs to be accurate and consistent and in a form suitable to its use. The information required to inform decisions about appropriateness of off-label use must be current and critically appraised to ensure efficacious and safe use once a medicine is approved for off-label use.

Information sources to support decisions about appropriateness of off-label uses could include the following. (This is not an exhaustive list and not presented in any particular order.)

1. Decisions of *competent regulatory bodies from other countries*.
2. *Secondary or summarised sources of high quality research evidence*.
3. *Evidence-based therapeutic guidelines and other medicines information sources*.
4. *Primary sources of high quality research evidence published in the peer-reviewed literature*.

Guiding Principle 2 describes the types of studies that should be sought and the need for rigorous evaluation of the validity, strength, clinical meaningfulness and applicability of the evidence.

5. *Pharmaceutical Industry*: Information from the pharmaceutical industry may be considered e.g. safety information (including any unpublished data) and additional information a company may have on off-label use of a particular medicine (which will only be available on direct request from the sponsor).

See Appendix 4 for specific examples of information sources.

Additional key point:

Secondary sources of summarised evidence, guidelines or other medicines information sources may have a number of limitations in this context: They are generally very variable in quality and currency, or not available in a sufficiently timely manner to provide useful guidance for very newly marketed medicines, where many off-label uses are frequently initiated in hospitals. They may also not provide useful information on comparative effectiveness, safety or cost-effectiveness. Therefore, rigorous review of primary research evidence is often needed to enable well informed decisions.

GUIDING PRINCIPLE 6

Monitor outcomes, effectiveness and adverse events.

The use of medicines off-label requires ongoing monitoring of use, outcomes and adverse events. The type of outcome evaluation, level of monitoring and review will vary with the category of off-label use (see Figure 1). These should be specified explicitly at the time of application to the DTC for approval. Specific measures for monitoring should be objective and measure clinically meaningful outcomes (effectiveness and safety). Monitoring should occur within a defined time period.

Outcomes should be evaluated prospectively, documented appropriately, and reported to the DTC, care providers and patients in a timely fashion. Regular review should occur to reduce the risk of continued use that is not efficacious or is unsafe.³¹ This information will assist DTCs in making further recommendations about ongoing approval for use of off-label medicines.

Health professionals should report adverse drug events to both the DTC and the TGA. Patients should also be advised of their ability to report any adverse medicine events directly to TGA. For new medicines or new uses, systematically collected outcome data should be reported in the peer-reviewed literature to add to the body of knowledge about the medicine. Advice should be sought from the institutional Human Research Ethics Committee to facilitate the ethical conduct of this evaluation.

ROUTINE USE

Prospective evaluation of clinical outcomes and/or use may be required in specific circumstances. For example, evaluation of the longer term safety of a newly marketed medicine (e.g. in special populations); monitoring of use to ensure it is consistent with DTC approval criteria (e.g. for high-cost or high-risk medicines); and monitoring of adverse events (e.g. for high-risk medicines or high-risk populations).

EXCEPTIONAL USE

Prospective evaluation of clinical outcomes (safety and effectiveness) should occur in all cases routinely. Monitoring of use should also occur in all cases to ensure it is consistent with DTC approved criteria (including ensuring that requirements for written informed consent are met).

CONDITIONAL USE

Prospective evaluation of clinical outcomes (safety and effectiveness) should occur in all cases routinely. Monitoring of use should also occur in all cases to ensure it is consistent with DTC approved criteria (including ensuring that requirements for written informed consent are met).

Prescribers are responsible for ensuring appropriate evaluation and monitoring for effectiveness and adverse events is undertaken. This must involve all those who are involved in caring for the patient and the patient. Institutional support to enable this to occur would be optimal.

GUIDING PRINCIPLE 7

Consider liability and accountability when using medicines off-label.

Although a medicine may be prescribed legally off-label, the prescriber, the DTC and the health service organisation may be exposed to a greater medico-legal risk.⁴⁷

If the off-label use of the medicine in a particular situation is accepted by the practitioner's peers as constituting competent professional practice, and the patient has given informed consent for its use, then prescribing off-label should not imply negligence (in the event of any harm). Whether a health professional is obliged (from a legal perspective) to inform the patient that the medicine is being used off-label will depend on the circumstances of each case.⁴⁸

It is important to provide detailed information about the medicine to the patient. Generally it is considered appropriate to advise the patient that the medicine will be used in an off-label manner and explain what this means.⁴⁷ As recommended in Guiding Principle 2, informed consent includes a discussion of the benefits, risks and alternatives. It is advisable to document this process and it may be necessary to obtain signed consent from the patient depending on the classification of off-label use (see Figure 1). As outlined in Guiding Principle 5, ongoing monitoring of use, outcomes and adverse events is recommended.

It is important that clinicians are well supported by hospitals in being able to readily access and source the information and evidence required to inform sound decision-making and appropriate use, and to undertake appropriate outcome evaluation, as recommended in these Guiding Principles.

References

1. O'Donnell CPF, Stone RJ, Morley CJ. Unlicensed and off-label drug use in an Australian neonatal intensive care unit. *Pediatrics*. 2002;110:e52.
2. Ballard CDJ, Peterson GM, Thompson AJ, Beggs SA. Off-label use of medicines in paediatric inpatients at an Australian teaching hospital. *J Paed Child Health*. 2013;49:38-42.
3. Ghinea N, Lipworth W, Kerridge I, Day R. No evidence or no alternative? Taking responsibility for off-label prescribing. *Intern Med J*. 2012;42:247-51.
4. Turner S. Unregistered and off-label drug use in paediatric inpatients. *Aust J Hosp Pharm*. 1999;29:265-8.
5. Gazarian M, Kelly M, McPhee J, Graudins L, Ward R, Campbell T. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust*. 2006;185:544-8.
6. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Saf* 2006;5:703-18.
7. Dresser R, Frader J. Off-label prescribing: a call for heightened professional and government oversight. *J Law Med Ethics*. 2009;37:476-86.
8. Stafford RS. Regulating off-label drug use — rethinking the role of the FDA. *N Engl J Med*. 2008;358:1427-9.
9. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Saf* 2006;5:703-18.
10. Gazarian M. Off-label use of medicines in the paediatric population: recommendations for assessing appropriateness. Discussion paper for consultation. 7 May 2007. Geneva: WHO Expert Consultation on Essential Medicines for Children; 2007. http://archives.who.int/eml/expcom/children/INDEX_children_07-2.htm
11. Aagaard L, Hansen EH. Prescribing of medicines in the danish paediatric population outwith the licensed age group: characteristics of adverse drug reactions. *Br J Clin Pharmacol*. 2011;71:751-7.
12. Neubert A, Dormann H, Weiss J, et al. The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Safety*. 2004;27:1059-67.
13. Santos DB, Clavenna A, Bonati M, Coelho HLL. Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. *Eur J Clin Pharmacol*. 2008;64:1111-18.
14. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA*. 2003;290:905-11.
15. Schreiner M. Paediatric clinical trials: redressing the imbalance. *Nat Rev Drug Discov*. 2003;2:949-61.
16. Hoppu K, Anabwani G, Garcia-Bournissen F, Gazarian M, Kearns GL, Nakamura H, et al. The status of paediatric medicines initiatives around the world—what has happened and what has not? *Eur J Clin Pharmacol*. 2012;68:1-10.
17. McNamara S. Drug labels still exclude kids. *MJA InSight* [serial on the Internet]. 2012. Available from: <https://www.mja.com.au/insight/2012/18/drug-labels-still-exclude-kids>.
18. Lowinger J, Gazarian M. “National guiding principles for off-label use of medicines” a project proposal for consideration by the National Medicines Policy Executive and Committee: Council of Australian Therapeutic Advisory Groups; 2012.
19. European Medicines Agency. Evidence of harm from off label or unlicensed medicines in children. London: European Medicines Agency; 2004. www.ema.europa.eu/
20. Aledort L. Off-label use of recombinant activated factor viii-safe or not safe? *N Engl J Med*. 2010;363:1853-4.
21. Sailler L, Attane C, Michenot F, et al. Rituximab off-label use for immune diseases: assessing adverse events in a single-centre drug-utilization survey. *B J Clin Pharmacol*. 2008;66:320-2.
22. Mason J, Pirmohamed M, Nunn T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. *Eur J Clin Pharmacol*. 2011;68:21-8.
23. American Academy of Pediatrics, Committee on Drugs. Uses of drugs not described in the package insert (off-label uses). *Pediatrics*. 2002;110:181-3.
24. Ruble J. Off-label prescribing of medications for pain: maintaining optimal care at an intersection of law, public policy, and ethics. *J Pain Palliat Care Pharmacother*. 2012;26:146-52.
25. McLay JS. A prospective questionnaire assessment of attitudes and experiences of off label prescribing among hospital based paediatricians. *Arch Dis Child*. 2005;91:584-7.
26. To TH, Agar M, Shelby-James T, Abernethy AP, Doogue M, Rowett D, et al. Off-label prescribing in palliative care - a cross-sectional national survey of palliative medicine doctors. *Palliat Med*. 2012;27:320-8.
27. Chen DT, Wynia MK, Moloney RM, Alexander GC. U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. *Pharmacoepidemiol Drug Saf*. 2009;18:1094-100.
28. NSW Health. Policy Directive: Medicine - evaluation of medicines for use in public hospitals. PD2008_037. 2008 [10 January 2013]; Available from: http://www.health.nsw.gov.au/policies/pd/2008/PD2008_037.html.
29. Transport Accident Commission. Non-established, new or experimental treatment policy (NENET) evidence summary. Melbourne: Victorian Government; 2009.
30. Faculty of Pain Medicine. Use of “Off Label” or drugs beyond licence in pain medicine. Australian and New Zealand College of Anaesthetists; 2007 [10 January 2013]; Available from: <http://www.fpm.anzca.edu.au/resources/educational-documents/documents/use-of-off-label-drugs-or-beyond-licence>.
31. Ansani N, Sirio C, Smitherman T, et al. Designing a strategy to promote safe, innovative off-label use of medications. *Am J Med Qual* 2006;21:255-61.

-
32. Gillick MC. Controlling off-label medication use. *Ann Intern Med.* 2009;150:344-7.
 33. Largent EA, Miller FG, Pearson SD. Going off-label without venturing off-course. evidence and ethical off-label prescribing. *Arch Intern Med.* 2009;169:1745-7.
 34. Ray W, Stein C. Reform of drug regulation - beyond an independent drug-safety board. *N Engl J Med.* 2006;354:194-201.
 35. Taylor P. Overseeing innovative therapy without mistaking it for research: a function-based model based on old truths, new capacities, and lessons from stem cells. *J Law Med Ethics.* 2010;38:286-302.
 36. Verhagen CC, Niezink AGH, Engels YY, Hekster YYA, Doornebal JJ, Vissers KCP. Off-label use of drugs in pain medicine and palliative care: an algorithm for the assessment of its safe and legal prescription. *Pain Pract.* 2008;8:157-63.
 37. Guyatt G, Sackett D, Cook D. How to use an article about therapy or prevention. A. Are the results of the study valid? *JAMA.* 1993;270:2598-601.
 38. Guyatt G, Sackett D, Cook D. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? *JAMA.* 1994;271:59-63.
 39. Levine M, Walter S, Lee H, et al. How to use an article about harm. *JAMA.* 1994;271:1615-9.
 40. Oxman A, Cook D, Guyatt G. VI. How to use an overview. *JAMA.* 1994;272:1367-71.
 41. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ.* 2001;323:334-6.
 42. National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Handbook series on preparing clinical practice guidelines. Canberra: NHMRC; 2000.
 43. Craig JC, Irwig LM, Stockler MR. Evidence-based medicine: useful tools for decision making. *Med J Aust* 2001;174:248-53.
 44. Dans AL, Dans LF, Guyatt GH, Richardson S. How to decide on the applicability of clinical trial results to your patient. *JAMA.* 1998;279:545-9.
 45. van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, Benninga MA. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics.* 2011;127:925-35.
 46. Australian Commission on Safety and Quality in Health Care. Safety and quality improvement guide. Standard 1: governance for safety and quality in health service organisations. Sydney: ACSQHC; 2012.
 47. Haysom G. Personal Communication. Avant Mutual Group Limited; 2013.
 48. Brooke-Cowden J. Personal Communication. MDA National Insurance Pty Ltd; 2013.

Appendices

APPENDIX 1: How these guiding principles were developed

These Guiding Principles were prepared by a Project Team, convened by CATAG, with funding support from NPS MedicineWise. The Project Team reviewed the published literature and synthesised concepts and themes from key work on off-label medicines use.

A first draft of the Guiding Principles was prepared by the Project Team and discussed by a specially convened Expert Advisory Group (EAG). The EAG was comprised of individuals with recognised expertise in a range of areas, such as therapeutics, QUM, evidence-based medicine, clinical medicine and pharmacy (adult and paediatric), nursing and consumer issues. Clinicians from therapeutic areas with high rates of off-label medicines use were included.

A face-to-face meeting of the EAG was held on 7 May 2013, following which a second draft of the Guiding Principles was prepared and circulated to the EAG for further comment. The EAG was also invited to make suggestions about organisations to engage in a wider stakeholder consultation and make recommendations for future work (see Appendix 2).

Medico-legal advice was sought from national medical indemnity organisations.

The Project Team reviewed all comments provided by the EAG and other informants and prepared a third draft for review by CATAG. Additional comments provided by CATAG were reviewed by the Project Team and another iteration of the Guiding Principles was prepared.

External consultation with key national organisations occurred during August and September 2013. The majority of respondents indicated their support for the broad principles and some suggested content modifications and prioritisation of future areas of work (see Appendix 2). All comments were collated and reviewed by the Project Team and changes made to the document. This version was sent to the EAG for review, with discussion occurring via teleconference and email correspondence in late September and early October 2013. Any disagreements were resolved by discussion among the Project Team and, if necessary, with individual members of the EAG. A final version was approved by the EAG and CATAG.

These guiding principles build on key concepts from the following previous work.

- › Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: Consensus recommendations for evaluating appropriateness. *MJA* 2006;185:544-48
- › Gazarian M. Off-label use of medicines in the paediatric population: recommendations for assessing appropriateness. Discussion paper for consultation, 7 May 2007. [WHO Expert Consultation on Essential Medicines for Children, 9-13 July 2007, Geneva] Available at http://archives.who.int/eml/expcom/children/INDEX_children_07-2.htm (accessed 18 June 2013)
- › Lowinger J, Gazarian M. "National Guiding Principles for Off-label Use of Medicines". A project proposal for consideration by the National Medicines Policy Executive Committee: Council of Australian Therapeutic Advisory Groups, 2012.

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- › NPS MedicineWise
- › Society of Hospital Pharmacists of Australia
- › Medicines Australia
- › Consumers Health Forum of Australia
- › Women’s and Children’s Healthcare Australasia
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- › Australian College of Midwives
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- › Australian Medicines Handbook Pty Ltd
- › Avant Mutual Group Limited
- › MDA National Insurance
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- › Statewide Therapeutic Drug Committee, TAS
- › NSW Therapeutic Advisory Group
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- › Dr Jocelyn Lowinger, National Co-ordinator, CATAG (to May 2011)
- › Mr Steve Morris, Chair, CATAG

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APPENDIX 2: Recommendations for the future

The following four areas were prioritised for action by the majority of respondents to the external consultation held during August and September 2013.

- › Develop a generic information leaflet and consent form for prescribers to share and use with patients/carers when discussing off-label use of medicines.
- › Develop education and training tools for prescribers and other decision-makers to:
 - a. raise awareness of the issues pertaining to the off-label use of medicines
 - b. develop skills to support evidence-based decision-making and the quality use of off-label medicines by health professionals.
- › Develop an off-label use of medicines registry. This would enhance pharmacovigilance to guide future use of these medicines. It could also assist in developing new information/research to enable changes to the product information.
- › Create a centralised evidence-evaluation (and/or decision-making) process for selected types of off-label uses, e.g. high-cost or high-risk medicines, vulnerable populations.

Other recommendations for future areas of work include:

- › Develop a minimum dataset to collect information on off-label medicine use for monitoring and evaluation purposes.
- › Make outcome data open access, combine with other sites/collaboratives and add to the evidence base, and if favourable, advocate for updating the registration of the medicine(s).
- › Explore applicability of general principles to other situations e.g. assessing appropriateness of a medicine's use as part of product familiarisation or expanded access programs.
- › Explore applicability of general principles to other settings, e.g. community, private hospitals, medicines information or therapeutic guideline developers.
- › Expand the principles to address the full spectrum of considerations relevant to unlicensed medicines use.

APPENDIX 3: Types of studies and research evidence needed to evaluate off-label use of medicines in the paediatric population

[Reproduced from: Gazarian M. Off-label use of medicines in the paediatric population: recommendations for assessing appropriateness. Discussion paper for consultation. Pages 13 - 16, 7 May 2007. Geneva: WHO Expert Consultation on Essential Medicines for Children; 2007. http://archives.who.int/eml/expcom/children/INDEX_children_07-2.htm] © Madlen Gazarian.

ASSESSING APPROPRIATENESS: EVALUATION OF EVIDENCE

RECOMMENDATIONS

At a global level, deciding whether use of a particular medicine in the paediatric population is appropriate should revolve around answering the question “*Is there high quality evidence supporting its use in the paediatric population*”, rather than on its regulatory approval status in a particular country. It is also worth noting that while data supporting regulatory approval is useful, it does not usually provide sufficient information to support therapeutic decision making in all clinical contexts, (40) as discussed below.

The answer to this question should be derived from a critical evaluation of the best available patient-based research evidence about *clinical effectiveness* and *safety*, ideally from clinical studies conducted in the relevant paediatric population (and ideally using age-appropriate paediatric formulations of high quality). The overall aim is to determine whether a particular medicine has an overall favourable *benefit vs. risk* ratio to justify any use in children, at an individual or population level. In order to justify routine and widespread use, additional information about *cost-effectiveness* for the relevant context in which use will occur is also needed. If a number of alternatives are available to treat a particular condition (including newly marketed medicines), evidence from comparative studies should be sought and the medicine with a *demonstrated advantage* in clinical effectiveness and/or safety and/or cost-effectiveness over other available alternatives should be chosen as the preferred agent for routine use.

Some of the needed information may be obtained from drug regulatory agencies and information in drug labels (e.g. efficacy and limited safety information) from competent authorities (e.g. FDA, EMEA). The lack of such labeling information, however, would not necessarily mean that the evidence does not exist and so the published literature (or other valid sources) should be searched to locate relevant studies of effectiveness and safety in the paediatric population. Available high quality evidence from anywhere in the world could inform decisions about use at a global level, unless there are valid reasons (e.g. important genetic, racial differences) to seek evidence from studies conducted in specific regions or in specific populations.

Information about *comparative* clinical effectiveness/safety and cost-effectiveness will need to also be sought from the published literature (or other valid sources) as these considerations, which are fundamental to rational use, are generally not within the remit of drug regulatory agencies and so are not part of assessments for marketing approval.(40)

The assessments referred to above should be primarily informed by appropriate high quality scientific *evidence*. However, expert

judgements will need to be exercised in order to decide what type of evidence might be appropriate for a given health issue or context; to evaluate its validity as well as to interpret its clinical meaningfulness and decide on its applicability to relevant paediatric health issues and contexts. *The people and processes through which such assessments are conducted to ensure that sound decisions are ultimately reached will need to be carefully discussed and explicitly defined (see section 8).*

Evaluating effectiveness

The level of rigour of this evaluation should be similar to that used by competent drug regulatory agencies (e.g. FDA, EMEA) for the clinical evaluation of medicines submitted for marketing approval. Important considerations include the *types* of studies (e.g. RCT, observational, or PK, PD); the *quality* of the study (independent of study type); the *validity* and *strength* of evidence; and its *applicability* to the relevant paediatric population (e.g. defined by different ages or disease states). Accepted guidelines for critical appraisal of therapeutic studies, for grading of “strength of evidence” and for deciding about applicability of research evidence to different patient circumstances can be used in answering this question.(41) (42)

The randomised controlled clinical trial (RCT) is widely accepted as the gold standard study design for determining the effectiveness of interventions, with some exceptions. (43) While high quality RCTs remain the ideal, they do have a number of acknowledged limitations, especially those performed specifically for gaining marketing approval.(40) These include relatively small numbers of included subjects (especially in published paediatric RCTs(44)) and short duration of follow-up, both of which limit their usefulness in determining effectiveness (and safety), especially in the treatment of chronic childhood conditions. In addition, subjects included in RCTs are often homogeneous and results may not be generalisable to the general paediatric population. A particular example of this is the issue of the different age groups that are encompassed by paediatrics (neonates; infants; children; and adolescents). There are large variations in drug handling and response between these age groups and so studies conducted in the relevant age groups are needed to inform decisions about medicines intended for use in that age group. Systematic reviews of RCTs may be able to overcome some but not necessarily all of these limitations.

A number of innovative trial designs have been developed to facilitate the study of small numbers of patients, which are particularly relevant for the study of uncommon or rare but serious childhood diseases. These include adaptive designs, such as Bayesian sequential studies;(45) randomized withdrawal designs;(46) the randomized placebo phase design;(47) and “n of 1” studies for populations.(48) Some of these study types may offer additional advantages over traditional RCTs,

Appendices

such as helping determine optimal patient and dose selection. Studies using such designs have been conducted in the paediatric population and should be sought to inform treatment decisions where available. While such studies are currently not numerous, it can be anticipated that their number is likely to increase in the future as more paediatric medicines research networks are established and become operational to address the increasing demand for better evidence about medicines for use in the paediatric population.

Another important aspect of assessing effectiveness is whether outcomes that are clinically meaningful to the paediatric population have been evaluated in a particular study.(49) These may include patient-based outcomes such as symptom scores or quality of life measures (validated in the relevant paediatric population) or paediatric specific ones, such as developmental, learning and behavioural outcomes. In some cases, a well designed and conducted observational study (e.g. prospective cohort study) evaluating clinically meaningful outcomes at relevant time points may be preferable to a RCT that does not possess these features.(50, 51) Cost-effectiveness may also be usefully assessed in high quality observational studies.(52) Although the role of observational studies in the evaluation of treatments has been a long-standing point of controversy,(53) judicious use of data from high quality observational studies to address relevant clinical questions (e.g. assessing effectiveness in real-life settings vs. efficacy under ideal circumstances; and meaningful safety assessments, see below) will be important. The need to explore the potential of alternative valid methodologies to investigate the safety and efficacy of new drugs under certain circumstances(54) is a persuasive argument that is especially relevant for the paediatric population.

Finally, regulatory agencies such as FDA and EMEA make provision for extrapolation of efficacy data from clinical studies in adults when certain specific conditions and assumptions are met. For example, if similar systemic exposure in adult and paediatric patients can be assumed to produce similar efficacy, then only PK data from the relevant paediatric population may be needed to allow extrapolation of efficacy data from clinical studies in adults. Where the existence of such PK and clinical effect relationships are clearly demonstrated, use of such data seems reasonable. However, such relationships may be more often assumed rather than demonstrated and so caution is recommended in judging the validity and applicability of this type of data. This caution is especially pertinent to any extrapolations about safety since many adverse drug reactions (especially the more serious ones) are not dose related and so would not be expected to be correlated with systemic drug exposures. Furthermore, as has been previously discussed, medicines may have a very different adverse reaction profile (type and frequency) in the paediatric population. These may be due to unpredictable mechanisms and so could only be detected through relevant clinical studies.

Evaluating safety

RCTs also have a number of limitations with regard to safety evaluation. First, as referred to above, the relatively small numbers of subjects in most RCTs mean that only the more common types of ADRs have any chance of being detected, even in a high quality RCT. For example, in order to be able to detect an ADR that might have an occurrence rate of 1 in 500,

approximately 1,500 subjects need to have been exposed in order to have 95% probability of detecting that event.(55) Most paediatric RCTs are considerably smaller in size(44) and so do not have much chance of being able to detect uncommon or rare ADRs, some of which may be severe or serious and have major impact on treatment decisions if known. Second, the limited duration of most RCTs mean that ADRs that may be related to prolonged exposure or cumulative dose as well as those that may have delayed or latent onset will also not be detected. This issue is especially relevant in paediatrics as many medicines are used long term (e.g. anti-asthma medicines, treatments for ADHD) or in periods of continuing organ development (e.g. younger children) and so data about safety outcomes, especially on paediatric relevant outcomes (e.g. growth, neurodevelopment, school performance) in typical patterns of use are crucial to inform treatment decisions. Third, evaluation of relevant safety outcomes in most RCTs is much less rigorous and complete than efficacy outcomes,(56) so even common ADRs that do have a good chance of being detected may not be. Finally, all of these inherent limitations in design are further compounded at the reporting stage, with evidence indicating that there is selective reporting of outcomes in most RCTs, leading to an overestimate of benefits vs. risks of a particular intervention.(57) This is especially so with RCTs that are sponsored by the pharmaceutical industry.(58)

Existing guidelines and systems for ranking evidence are also focused mostly on efficacy evaluation and so RCTs are considered the highest quality study design. However, the types of studies that should be sought with regard to evaluating the full spectrum of safety of a particular medicine are broader. In many instances only observational studies (e.g. cohort or case-control studies) from post-marketing surveillance, rather than randomized controlled trials, or meta-analyses, will provide the necessary data. This applies particularly to rare, but potentially serious, adverse effects (e.g. serious sepsis and death associated with anti-tumour necrosis factor therapy) or those which manifest following prolonged exposure (e.g. growth retardation with steroids) or following a long latent period (e.g. infertility following cancer chemotherapy in childhood).

Therefore, in order to build a *composite* picture of the overall safety profile of a particular medicine in the paediatric population, evidence from a number of different sources needs to be collated. These sources will include RCTs (published and unpublished), systematic reviews, observational studies (e.g. cohort and case control) as well as information from post-marketing surveillance (including voluntary ADR reporting systems and database linkage studies). This type of systematic collation of safety information is a very important step in both the initial and ongoing evaluation of the overall benefit vs. risk and appropriateness of use (approved and unapproved), but is currently not occurring systematically, especially for unapproved medicines used in children. Addressing this unmet need will be even more important in the current climate of increased medicines research in certain parts of the world, sometimes revealing important safety information, but not necessarily reflected in regulatory approval status or paediatric prescribing information available in other parts of the world in a timely way. It is increasingly recognised that knowledge about the risks and benefits of a medicine changes over its lifetime and must be better understood in order to ensure patient safety.(59)

APPENDIX 4: Examples of information sources to support decisions about appropriate use of off-label use of medicines

(For use in conjunction with Guiding Principle 5)

1. Decisions of competent regulatory bodies from other countries:
 - US Food and Drug Administration (FDA) (<http://www.fda.gov/>)
 - European Medicines Agency – European public assessment reports (http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp)
 - NZ Medsafe (<http://www.medsafe.govt.nz/>)
2. Secondary or summarised sources of high quality research evidence:
 - Cochrane database of systematic reviews
 - UK National Institute for Health and Care Excellence (NICE) Evidence summaries: <http://www.nice.org.uk/mpc/evidencesummaries/unlicensedofflabelmedicines/home.jsp>
 - The US Agency for Healthcare Research & Quality (AHRQ) www.ahrq.gov
 - The Canadian Agency for Drugs and Technologies in Health (CADTH) www.cadth.ca
 - UpToDate (<http://www.uptodate.com/home/product>)
3. Evidence-based therapeutic guidelines and other medicines information sources:
 - National Health and Medical Research Council
 - Therapeutic Guidelines Ltd
 - Australian Medicines Handbook (AMH) / AMH Children's Dosing Companion
 - British National Formulary / British National Formulary for Children
 - eviQ (<https://www.eviq.org.au/>)
 - Specialty Societies practice guidelines, for example Palliative Care Guidelines
 - NSW TAG therapeutic review documents and position statements <http://www.ciap.health.nsw.gov.au/nswtag/reviews/lit-reviews.html>

Note: Secondary sources of summarised evidence, guidelines or other medicines information sources may have limitations. They are generally variable in quality and currency or not available in a timely manner to provide useful guidance for newly marketed medicines, where many off-label uses are frequently initiated in hospitals. They may also not provide useful information on comparative effectiveness, safety or cost-effectiveness. Therefore, rigorous review of primary research evidence is often needed to enable well informed decisions.

