CATAG
Council of Australian Therapeutic Advisory Groups

Rethinking medicines decision-making

GUIDING PRINCIPLES FOR THE OFF-LABEL USE OF MEDICINES IN AUSTRALIAN HEALTHCARE SETTINGS

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EXECUTIVE SUMMARY

The *Guiding Principles for the Off-Label Use of Medicines in Australian Healthcare Settings (Version 2, June 2026)* provide a national framework to support safe, effective, and evidence-informed decision-making when prescribing and using medicines outside their Therapeutic Goods Administration (TGA)-approved Product Information (PI).

The Council of Australian Therapeutic Advisory Groups (CATAG) originally produced this guidance document in 2013 and updated the Guiding Principles in 2026. The updates were made to further emphasise the importance of a structured, evidence-informed, and patient-centred approach to the safe, consistent, and responsible use of medicines off-label across all healthcare settings.

In these Guiding Principles 'off-label use' is defined as prescribing and using a medicine, which is included in the Australian Register of Therapeutic Goods (ARTG), for a purpose or in a manner that differs from that stated in its TGA-approved PI (or outside ARTG approved conditions), such as for an unapproved indication, dose, route, population, or formulation. Off-label use of medicines is a well-recognised and often necessary aspect of clinical practice in Australia. It may represent best practice and/or the only viable treatment option in certain populations such as paediatrics, rare diseases, and palliative care. However, such use is typically supported by less robust evidence and may carry increased uncertainty regarding safety, effectiveness, cost-effectiveness, and medico-legal risk.

The clinical, safety, ethical, legal and financial issues related to the off-label use of medicines, require a careful and responsible approach to support 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 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 benefit: harm ratio for the intended clinical use and population. Clinicians need to evaluate the available evidence when considering off-label use of a medicine. Clinicians should seek appropriate, and where needed independent, expert advice when considering off-label use outside routine practice to support decision-making based on robust evidence.

These Guiding Principles are intended to guide the decision-making process, based on a systematic evaluation of the evidence of benefit and harm of the proposed use. The following four categories of off-label use are defined within these Guiding Principles:

- routine use
- exceptional/individual use
- conditional use
- research or investigational use.

They depend on the strength and quality of supporting evidence and clinical circumstances. Use is not recommended when a proposed off-label use does not fall into one of the above four categories.

Off-label use places heightened responsibility on clinicians to make decisions are evidence-based, clinically justified, and aligned with professional standards. It carries increased legal and professional risk, requiring clinicians to be familiar with relevant laws, guidelines, and competency frameworks, and to confirm appropriate indemnity arrangements. These Guiding Principles contain recommendations for informed consent, monitoring and outcome evaluation for each category of off-label use of medicines.

The document aims to support clinicians, consumers, and health services across hospitals and primary care settings to make consistent, high-quality decisions regarding off-label use of a medicine. It complements existing regulatory and clinical frameworks by outlining additional responsibilities and safeguards specific to off-label use.

GUIDING PRINCIPLES

The overarching guiding principles are:

Guiding Principle 1
Consider off-label use of medicines when other medicines included in the ARTG for the condition are less suitable, unavailable, exhausted or not tolerated.

Guiding Principle 2
Use the highest quality, strongest and most clinically relevant evidence available to determine the appropriateness of off-label use of a medicine.

Guiding Principle 3
Seek expert input when considering off-label use outside of routine practice.

Guiding Principle 4
Involve the consumer in shared decision-making and document informed consent when recommending the use of a medicine off-label.

Guiding Principle 5
Provide and facilitate access to appropriate information regarding the off-label use of medicines at transitions of care.

Guiding Principle 6
Monitor and document the off-label use of medicines.

Guiding Principle 7
Evaluate the off-label use of medicines and disseminate the results and outcomes.

Guiding Principle 8
Consider the legal and professional responsibilities relevant to off-label use of medicines.

OVERVIEW

PURPOSE

The purpose of these Guiding Principles is to provide a framework that supports the quality use of medicines used off-label across Australian public and private hospitals and in primary care. These principles seek to assist clinicians, consumers and health services in making informed decisions about the evaluation, approval and use of medicines off-label.

DEFINITION

For the purposes of these Guiding Principles, the term "*off-label*" refers to the use of a medicine, which is included in the Australian Register of Therapeutic Goods (ARTG), for a purpose or in a manner that differs from that stated in its Therapeutic Goods Administration (TGA)-approved Product Information (PI). This includes situations where a medicine is prescribed, supplied or administered:

- for a different indication
- at a different dose
- via an alternate route of administration
- to an individual whose characteristics are outside the registered use (for example a different age)
- in a dosage form that is prepared or modified in a way that does not align with the preparation directions provided in the PI.

"Off-label" does not include the use of a medicine that is not included in the ARTG by the TGA (an "unapproved medicine").

BACKGROUND

KEY POINTS

- A medicine can only be marketed in Australia after it has been included in the ARTG, unless an exemption applies under the Therapeutic Goods Act 1989.
- A medicine included in the ARTG is approved for use in accordance with its TGA-approved PI. Use of the medicine outside the scope of its TGA-approved PI is considered off-label.
- Off-label use is well-recognised in clinical practice and may represent the most appropriate or prevailing standard of care in certain populations.
- Off-label use may be supported by varying levels of evidence and is subject to less formal scrutiny than on-label use. Where evidence is limited, this potentially creates less certainty about benefit, harm and cost-effectiveness.
- Off-label use carries additional professional, ethical and medico-legal considerations, including increased requirements around informed consent, documentation and communication across transitions of care.
- Off-label use can have financial implications for consumers, and Australia's health system.
- A structured, evidence-informed approach to off-label use is critical to uphold the principles of Quality Use of Medicines (QUM) and minimise unintended harm.

To market a medicine product in Australia, a sponsor (typically a pharmaceutical company) must apply to the TGA for that product to be included in the ARTG. The application specifies the proposed indications for use, doses and routes of administration.[1] It may also specify subpopulations by age, sex or other relevant characteristic.[1] The TGA evaluates the evidence supporting the medicine's safety and efficacy for the proposed use, as well as the quality of the product.[2] If requirements are met, the medicine product is entered in the ARTG.[2] Once included in the ARTG, the sponsor can market and supply the medicine in Australia, and its approved indications and other regulatory details are reflected in the PI.

The indications for which the sponsor seeks TGA approval may be influenced by several factors, including commercial considerations of the sponsor. This means that the TGA-approved PI may not encompass the full range of indications where there is evidence that the medicine could be used effectively and safely.[3, 4] Sponsors bear the full cost of the application process, which may make it economically unviable to seek approval (despite good evidence to support use) for indications with a small market (for example rare diseases), or for additional indications when new evidence becomes available. This is especially true for 'off-patent' medicines*. In some cases, the TGA may approve fewer criteria or indications than those sought by the sponsor in their application, including where the strength of the regulatory information presented to the TGA is insufficient to support approval. However, this does not preclude individual circumstances in which the medicine may be appropriate for use such as for an indication, dose or population group. In 2024, the TGA launched the **Medicines Repurposing Program**, which aimed to improve access by supporting applications for new therapeutic uses of existing medicines.[5, 6]

Once a medicine is included in the ARTG, its use in practice may extend beyond the uses included in the approved PI. This use of a medicine outside

of the approved PI is deemed "off-label".[7] Off-label use of medicines is a well-recognised clinical practice, particularly prevalent in specialist care settings and in populations and indications with limited or no approved treatment options.[8-12] It can provide access to additional treatment options through the use of existing medicines for new evidence-based indications, doses or routes,[8] and in some cases may represent the most appropriate therapeutic approach, or even the prevailing standard of care.[9] However, off-label use of medicines generally has less robust supporting evidence and may be subject to less rigorous evaluation of efficacy, safety and cost-effectiveness compared to the on-label use of a medicine (use of a medicine exactly in accordance with the approved PI as authorised by the TGA). Consequently, the balance of benefits and harms may be less well understood for the medicine's off-label uses.[13] Relative to on-label use, off-label use therefore has an increased risk of reduced therapeutic benefit and/or increased harms,[14-17] and inefficient use of scarce healthcare resources.[13]

Using or prescribing a medicine off-label in Australia is subject to medico-legal requirements and professional standards. The TGA does not generally seek to regulate clinical practice. Off-label use for treatment purposes is a clinical decision, made at the discretion of the treating clinician. The Therapeutic Goods Act 1989 regulates advertisements for therapeutic goods, including both approved and unapproved therapeutic goods. Further, under the Therapeutic Goods Act 1989, the promotion of approved goods for an off-label use is prohibited including where the advertisement is directed exclusively to health professionals. In accordance with the Medicines Australia Code of Conduct, a sponsor may engage in scientific exchange regarding off-label use of medicines, however this exchange must be non-promotional in nature.[18] As outlined in these Guiding Principles, to uphold **QUM** principles,[19] there are additional clinician responsibilities when using a medicine off-label. This includes clinical, medico-legal, consenting, financial, and ethical considerations.

When medicines are affected by a supply shortage in Australia, there tends to be an increase in the off-label use of other medicines to address gaps in supply (for example modifying a formulation for paediatric use or using another medicine for an off-label indication). This can cause a cascade of shortages as unexpected peaks in demand for substitute products occur. In addition, medicines shortages may be triggered or exacerbated by the off-label use of a medicine. A high volume of off-label use of a single medicine may result in higher-than-expected demand for the medicine causing it to fall into shortage and become unavailable to consumers who require it for the indication included in the ARTG. This highlights the potential broader implications of using a medicine off-label.

Studies indicate variability in awareness, knowledge and approaches to the off-label use of medicines among clinicians and decision-makers in health services,[9, 20, 21-23] highlighting the importance of clear national guidance and education for healthcare providers, including during their undergraduate training. Currently, clinicians face difficulties in identifying off-label use in practice when a medicine's off-label status is not visible within their clinical software systems. In addition, clinical software systems are not integrated (for example between primary care and hospital providers), which hampers communication regarding off-label use of medicines at transitions of care.

These Guiding Principles reflect the QUM principles and provide a decision-making framework to support clinicians to identify the off-label use of medicines and to then apply the necessary safeguards around it to support safe, effective and cost-effective use of these medicines.[19]

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* Medicines for which patent protection has expired, meaning the original sponsor no longer holds exclusive rights to manufacture or market the product.

SCOPE

These Guiding Principles apply to the use of medicines listed in the ARTG, in ways that are outside the parameters specified in the approved PI. This includes use for differing indications, doses, routes of administration and other conditions of use.

These Guiding Principles apply in all settings, where medicines are prescribed, initiated or administered off-label, including public and private hospitals as well as primary care.

Modification of dosage forms, outside of preparation directions provided in the PI is a form of off-label use and therefore these Guiding Principles apply in such circumstances. This includes extemporaneous compounding from a product included in the ARTG. Additional considerations also apply when modifying a dosage form which are not addressed within this document. These considerations include factors such as altered product stability, and the need for adherence to additional professional standards such as those that apply to the compounding of medicines, including the **TGA compounding guidance page** and Pharmacy Board of Australia's **Guidelines on compounding of medicines**.

Use of medicines not included in the ARTG ("unapproved medicines"), do not meet the definition of "off-label" use. The use of these medicines, accessed via other permitted mechanisms such as the TGA's Special Access Scheme, Authorised Prescriber scheme, clinical trials or personal importation is outside the scope of this document. While these guiding principles are generally applicable to the use of unapproved medicines, additional considerations apply including assessment of product quality and other medicolegal issues, which are not addressed here.

This document does not replace or alter existing regulatory and clinical requirements for medicines. The scope of this document addresses only additional or specific considerations relevant to off-label medicine use.

GUIDING PRINCIPLES

GUIDING PRINCIPLE 1

Consider off-label use of medicines when other medicines included in the ARTG for the condition are less suitable, unavailable, exhausted or not tolerated.

The principles of QUM, which underpin Australia's *National Strategy for Quality Use of Medicines* and the *National Medicines Policy*, should guide decision-making when considering the use of any medicine in the management of a medical condition.[19, 24] These principles emphasise that medicines should be selected and used judiciously, appropriately, safely, and effectively, based on the best available evidence and the individual's circumstances. Within this context, evidence-based off-label use of medicines is recognised as legitimate, appropriate, and, in many circumstances, standard clinical care. The absence of a specific TGA approved indication does not, of itself, indicate that the use of a medicine off-label is experimental, unsafe, or inappropriate.

In many areas of clinical practice off-label use of medicines is well established practice, supported by accumulated evidence and/or expert consensus and routinely incorporated into authoritative clinical guidelines. For certain populations and conditions, such as paediatrics, maternity, and palliative care, the availability of clinically appropriate medicines, included in the ARTG, may be limited. In these circumstances, off-label use frequently represents established practice and may constitute the only available and/or best treatment option for a specific population group, condition, or clinical scenario.

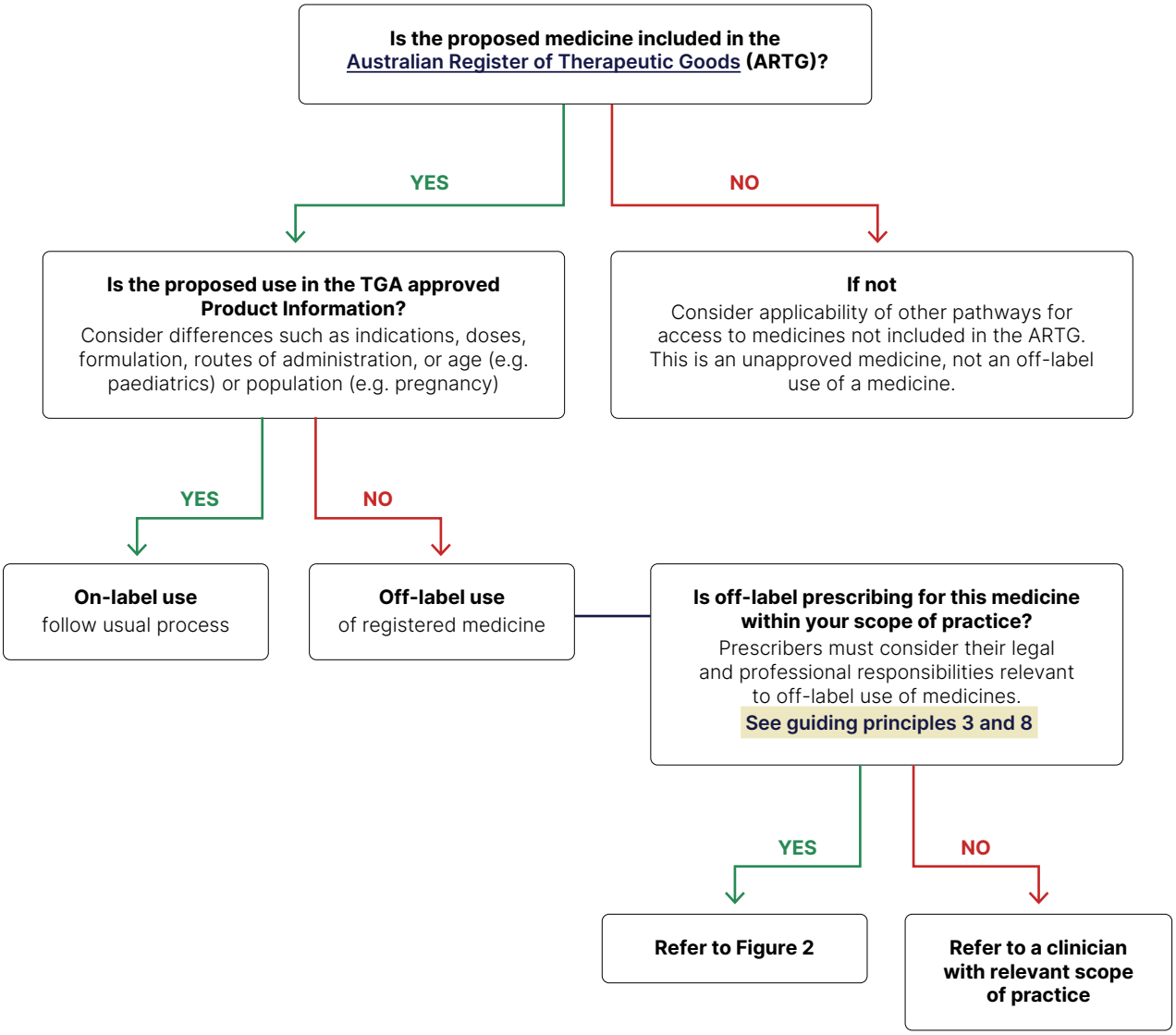
In alignment with the National Prescribing Competencies Framework, off-label use of a medicine may be considered when other treatment alternatives are unavailable or inappropriate.[25] This may include situations where on-label use of a medicine is:

- unavailable, including temporary unavailability due to a medicine supply shortage
- ineffective for the individual
- not tolerated by the individual
- contraindicated in the individual's circumstances (including consideration of excipients)
- deemed unsuitable for other justifiable reasons (including lack of accessibility for the individual)
- not the recognised standard of care.

Where there is a well-justified clinical need, a favourable individual-specific benefit versus harm assessment, and adequate evidence to support the intended use over available alternatives (see **Guiding principle 2**) off-label use of a medicine should be considered.

Figure 1 provides a potential decision pathway for identifying off-label use of medicines.

Figure 1: Decision pathway for identifying off-label use and scope of practice considerations.



GUIDING PRINCIPLE 2

Use the highest quality, strongest and most clinically relevant evidence available to determine the appropriateness of off-label use of a medicine.

Compared to on-label use of a medicine, off-label use has less robust evidence to support use and is often subject to less formal scrutiny. Clinicians are therefore responsible for considering the balance of potential benefits and harms within the clinical context, taking into account the strength and certainty of the available evidence as well as the individual's risk profile. These considerations should guide decisions about whether off-label use is appropriate. This includes responsibility to seek appropriate specialist expertise to inform sound judgements. Informed expert judgement 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.[26] Determining the strength and quality of evidence to support use will also inform the level of clinical and medicolegal safeguards required, such as the intensity of monitoring and how informed consent is documented.

When evaluating the evidence for off-label use of a medicine, clinicians also need to keep in mind the applicability of evidence to the individual. This is particularly relevant for populations where the medicine may have an altered safety profile or different pharmacokinetic and pharmacodynamic profiles such as pregnant people, paediatrics,[27] older people, and people from ethnic backgrounds not included in pivotal clinical trials. Ideally, efficacy or effectiveness and safety data derived from the relevant population should inform these evaluations.

In most cases it will be necessary to weigh the benefits and harms for the medicine against other potentially appropriate treatment options. This comparison should include not only other medicines, but also evidence-based non-pharmacological interventions (for example surgery, cognitive behavioural therapy) and, where appropriate, the option of no active treatment (for example disease surveillance). Comparative clinical effectiveness, safety and cost-effectiveness should be considered to determine whether the proposed off-label use offers a clear and justifiable clinical advantage.[27, 28] Consideration should also be given to the likely impact on quality of life.

Following assessment of the evidence the treatment with a clear advantage within the relevant population/ intended use, should be chosen.[27] Clinical superiority regarding efficacy and safety should be the primary consideration in decisions regarding medicine use, including off-label uses. Cost alone should not justify the selection of a clinically inferior option however affordability and budget impact should still be considered as part of the overall assessment, ensuring decisions remain sustainable within available resources.

Table 1 outlines four broad categories of off-label use and the supporting evidence required to classify any medicine used off-label within that category. It includes considerations for hospital and primary care-based initiation of the off-label use. This framework is intended as decision support guidance rather than prescriptive; the categories are not rigid legal classifications, and local governance arrangements may vary by jurisdiction.

Table 1: Framework for categorising proposed off-label use of a medicine

Strongest evidence base

Category	Characteristics	Supporting information	Hospital considerations	Primary care considerations†
ROUTINE USE				
Off-label use of medicines that in practice is considered consistently justified and sometimes described as established use supported by high-quality (level 1[29]) evidence.	High-quality evidence and rigorous review demonstrate safe, effective and cost-effective use. Use is characterised by an overall favourable benefit–harm balance for the intended clinical use and population.	Use is recognised in high-quality national and/or international guidelines‡ and evidence-based medicines resources such as Therapeutic Guidelines (TG®). See **Appendix 1** for further examples. High-quality (level 1[29]) evidence to support use such as: → high-quality systematic reviews or meta-analyses of randomised controlled trials → well-designed individual randomised controlled trials with narrow confidence intervals	Standard formulary inclusion possible. Examples: → Morphine for dyspnoea in palliative care (adults)[30] → Metformin for gestational diabetes[31]	Depending on supporting information, use may be considered routine practice. Example: → Amitriptyline as adjuvant therapy in pain management[32]
CONDITIONAL USE				
Off-label use of medicines for a specific cohort, where the benefit:harm profile is less clear, and therefore use is supportable only in a population sub-group defined by pre-specified criteria (for example disease sub-type and/or severity, age, comorbidities, prior treatment history and line in therapy) and according to an agreed protocol.	Low to moderate quality evidence, but potential benefits appear greater than potential harms and there is reasonable justification for use in select **population group**(s).	Typically use supported by moderate quality evidence such as: → high-quality cohort studies or systematic review of these → lower quality randomised controlled trials → individual case-control studies or systematic reviews of these	Restricted use via a protocol, medicines access program **(MAP)**, or included on formulary with defined restrictions. The conditions of use should include details on: → appropriate monitoring requirements → review timeframes to assess the appropriateness of continued therapy. Examples: → Atovaquone for Pneumocystis pneumonia (PCP) prophylaxis[33] → Prucalopride for constipation in paediatrics[34]	Clinicians who practice within a specific area may prescribe medicines within their scope of practice that fall into the "conditional use" category; however, prescribing should align with recognised standards of good medical practice (see **Guiding principle 3** and **Guiding principle 8**).

Continued →

† Scope of practice may not need to be considered if the off-label use of medicine is a continuation of treatment initiated by a Specialist or in hospital.

‡ Secondary sources of summarised evidence, guidelines or other medicines information sources may have limitations for use in decision-making regarding the off-label use of medicines that are newly registered. Evidence may lack the quality and currency needed to guide decisions for their use off-label. Secondary sources may also not provide adequate consideration or information on comparative effectiveness, safety or cost-effectiveness. Therefore, rigorous review of primary research evidence is often needed to enable well-informed decisions.

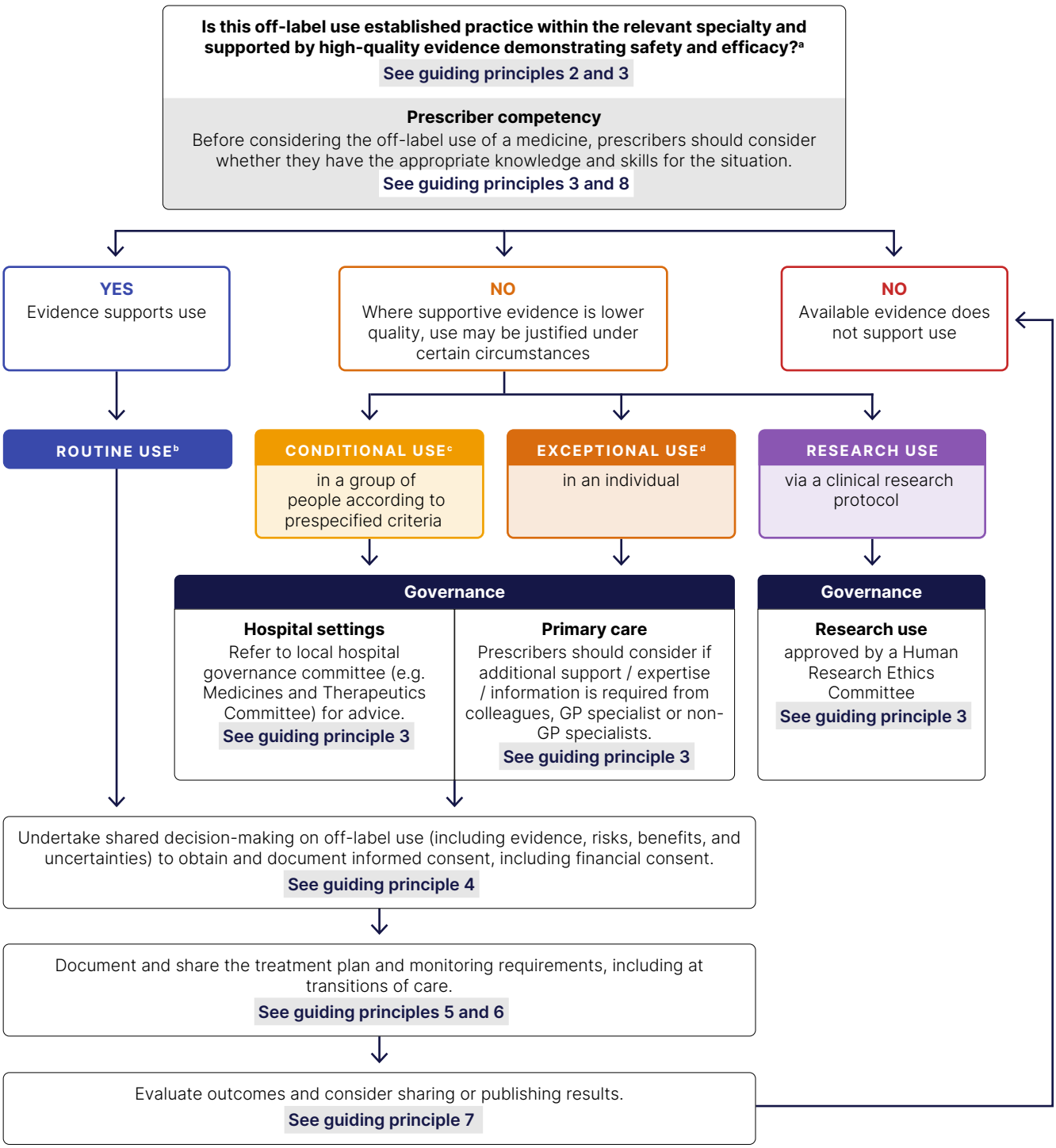
Category	Characteristics	Supporting information	Hospital considerations	Primary care considerations†
EXCEPTIONAL / INDIVIDUAL USE				
Off-label use for an individual where, taking into account individual specific factors, the treatment is likely to present the best possible benefit: harm profile of available treatment options, including non-drug treatment options.	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, such as a serious and/or rare condition with no alternative treatments available, tolerable or untrialled by the individual.	Use supported by low quality evidence such as → case series → low quality cohort or case-controlled studies → expert consensus based on non-systematic reviews of results → mechanistic studies → multiple published cases[35]	Case-by-case approval (such as individual patient use (IPU) / individual patient approval (IPA)) with/without a Medicines Access Program (MAP). IPU/IPA approval should include details on: → appropriate monitoring requirements → review timeframes to assess the appropriateness of continued therapy for the individual. Examples: → Ketamine (IV) for severe, treatment-resistant depression with suicidality.[36] → Botulinum toxin for rare dystonias or refractory neuropathic pain.[37]	Clinicians who practice within a specific area may prescribe medicines within their scope of practice that fall into the "exceptional use" category; however, prescribing should align with recognised standards of good medical practice and involve appropriate Specialist guidance (see **Guiding principle 3** and **Guiding principle 8**). Off-label uses supported by only lower strength/quality of evidence will generally require expert advice from the relevant specialist.
RESEARCH USE				
Off-label use with significant uncertainty regarding benefit:harm profile, but where there is potential for clinical benefit. Such use is investigational or experimental[38, 39] and should only occur within a clinical trial or under a research protocol endorsed by a Human Research Ethics Committee (HREC).	Low or very-low quality evidence or only a mechanistic rationale for efficacy, with uncertain benefits, and harms that are significant or unknown, but where there is potential for clinical benefit.	Limited or no supporting clinical evidence available.[35]	Use via a clinical research study which is reviewed and approved by a HREC. TGA's clinical trial schemes may apply. Example: → Acetyl-L-carnitine for myotrophic lateral sclerosis (ALS).[40]	
NOT RECOMMENDED				
	Low or very-low level of evidence with uncertain benefits or harms and/or when the available evidence indicates that the overall benefit: harm ratio is (or is expected to be) unfavourable for the intended clinical use or population.[20, 27]	Limited or no supporting clinical evidence available,[35] or evidence available confirms or suggests unfavourable benefit: harm ratio. No available clinical trial or endorsed trial protocol.	Use not supported, outside a clinical trial. Examples: → Idarucizumab to reverse anticoagulation for transition to elective surgeries.[41] → Quinine for restless legs or nocturnal cramps.[42]	

Weakest evidence base

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.

Figure 2 outlines a structured decision pathway for assessing the appropriateness of using a medicine off-label based on evidence, prescriber competency, and governance requirements.

Figure 2: Assessing appropriateness of off-label use of medicines.



[a] **High-quality (level 1) evidence** to support use such as systematic reviews or meta-analyses of randomised controlled trials and/or well-designed individual randomised controlled trials with narrow confidence intervals.

[b] **Routine use** recognised in national and/or international guidelines and evidence-based medicines resources such as Therapeutic Guidelines (TG®). See **Appendix 1** for further examples.

[c] **Conditional use** may be considered when there is 'low' to 'moderate' quality evidence, but potential benefits appear greater than potential harms and there is reasonable justification for use in select population groups.

[d] **Exceptional/individual use** may be considered when 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 and no treatments with higher quality evidence are available, tolerable or have been exhausted.

Adapted from Rethinking medicines decision-making in Australian Hospitals. Guiding principles for the quality use of off-label medicines. Council of Australian Therapeuticw Advisory Groups; 2013. © Copyright 2013.

ROUTINE USE

Routine use is likely to constitute a significant proportion of off-label use across hospital and primary care settings. Where the off-label use is determined to be routine use, no further examination of the evidence is required unless there are specific factors that may warrant more critical evidence evaluation, such as a comorbidity, renal impairment or age, that may impact the medicine's safety or efficacy.

In the primary care setting, where the routine off-label use is within the clinician's scope of practice, the treatment is likely appropriate for initiation, taking into consideration the requirements within these guiding principles such as informed consent.

In hospitals, where routine use is considered to be cost-effective, these treatments may be appropriate for inclusion on a hospital formulary.

EVALUATING THE EVIDENCE

Any off-label use outside of "routine use" will require a more in-depth appraisal of the available evidence. **Appendix 1** has been compiled to support evaluation of the evidence when off-label use is not recognised in national and/or international guidelines and/or evidence-based medicines resources.

In some institutions, access to off-label treatment options may require additional approval through an internal governance committee, such as a Medicines and Therapeutics Committee (MTC), especially for medicine use that falls into the "conditional" or "exceptional" categories for off-label use. Note: Approval may be sought prior to discussion with the person receiving care in certain circumstances, especially where individual factors need to be considered to avoid offering unfeasible options.

CONDITIONAL USE

In the primary care setting, it may be appropriate for clinicians who practice within a specific specialty area to prescribe medicines that fall into the "conditional use" category, when this is within their scope of practice. This prescribing, however, should align with recognised standards of practice (**Guiding principle 8**), involve appropriate specialist guidance where appropriate (**Guiding principle 3**) and follow other guidance provided within these guiding principles.

In hospitals, following critical appraisal of the available evidence, conditional off-label uses may be included on a hospital formulary, where the listing clearly defines the population group for whom the expected benefits outweigh the risks and/or specifies appropriate conditions of use. These conditions of use may include monitoring requirements, review timeframes or objective clinical outcomes that serve as minimum thresholds for continued therapy.

EXCEPTIONAL/INDIVIDUAL USE

Where off-label use of a medicine is categorised as exceptional/individual use, the treatment will likely only be appropriate for specialist initiation, and only following critical appraisal of the available evidence, including assessment of its applicability to the individual.

In primary care, continuation of a specialist-initiated medicine used off-label within this category may be appropriate, where the suitability of the off-label use should have already been critically appraised. This should be done with support and communication from the initiating specialist prescriber as outlined in **Guiding principles 5 and 6**. If there is a lack of clarity about the appropriateness of using the medicine off-label, primary care clinicians should review discharge summaries and supporting documentation, or seek direct clarification from hospital teams or specialist prescribers who initiated the medicine.

In hospitals, medicine use within this category is generally unsuitable for formulary listing and will typically require an individual patient (IPU/IPA) application if the consumer requires hospital subsidised access. Any IPU/IPA approval should include a review timeframe, any monitoring requirements to support MTC consideration of further therapy, and/or objective clinical outcomes that serve as minimum thresholds for considering further approval/continued therapy.

RESEARCH USE

Off-label use of a medicine that falls within the research use category should, where possible, occur as part of a formal clinical trial. This will add to the body of knowledge regarding the medicine and allow Human Research Ethics Committee (HREC) review of the research protocol.

§ Secondary sources of summarised evidence, guidelines or other medicines information sources may have limitations for use in decision-making regarding the off-label use of medicines that are newly registered. Evidence may lack the quality and currency needed to guide decisions for their use off-label. Secondary sources 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 3

Seek expert input when considering off-label use outside of routine practice.

Clinicians should seek appropriate and, where indicated, independent expert advice to guide decisions about off-label use and to confirm whether the available evidence is appropriate for the specific health issue or clinical context. Expert input may not be required where off-label use is well established and supported by high quality evidence and guidelines (for example routine use).

Independent experts can help decide what types of evidence are needed, evaluate the validity and clinical meaningfulness of the evidence and assess its applicability to the population group. This may include clinicians with specialist expertise in relevant therapeutic areas, as well as individuals with recognised capability in evaluating therapeutic evidence.

When the strength of evidence is limited, as is common in paediatrics and other special populations, seeking input from an interdisciplinary and, where appropriate, independent expert group is recommended. A range of perspectives supports more considered decision-making, particularly when balancing scarce data against significant unmet clinical needs.[28] This expertise may be accessed through a hospital MTC or via professional bodies or colleges, academia or other independent experts where appropriate.

↳ PRIMARY CARE SETTINGS

Primary care clinicians, (including medical and non-medical prescribers) prescribe medicines off-label, which often falls into the category of "routine use", as these medicines have high-quality evidence and are considered established practice recognised in therapeutic guidelines. Additionally, off-label use of medicines often reflects the continuation of hospital or specialist-initiated therapy,[43] where the suitability of the off-label use should have already been assessed. Information regarding this decision should be communicated to all clinicians at transitions of care and documented accordingly (see **Guiding principle 5**). If there is a lack of clarity about the appropriateness of using the medicine off-label, primary care clinicians should seek advice from the hospital or the specialist who initiated the medicine.

Clinicians initiating off-label use of a medicine in primary care are expected to meet the same standard of practice as in other healthcare settings and should apply these guiding principles, noting that, unlike in hospital settings, off-label medicine use is often undertaken without organisational medicines governance support. It is important for the primary care clinician to consider their own knowledge and expertise in the relevant clinical area in determining the need to seek input from colleagues.

This is particularly important for special populations (see **Guiding principle 2**) where the evaluation of evidence and specific considerations relevant to these populations require appropriate specialist expertise (also see points below regarding hospital settings).

↳ HOSPITAL SETTINGS

Where detailed evidence evaluation and synthesis is required, inclusion of individuals with expertise in critical appraisal of evidence is important, as clinical expertise and expert opinion alone are insufficient.[28] Clinicians within hospital settings should therefore seek review and approval from MTCs for the off-label use of a medicine, except when the off-label use of a medicine is considered routine use. For more details, refer to **Achieving effective medicines governance: Guiding Principles for the roles and responsibilities of Medicines and Therapeutics Committees in Australian hospitals**.

The evaluation of medicines used off-label, when outside of routine use, is best conducted by people with an appropriate range of expertise, including:[28]

- → methodological expertise such as evidence-based medicine, clinical epidemiology, pharmacoepidemiology, pharmacovigilance, clinical pharmacology and pharmacoeconomics
- → clinical and therapeutic expertise:
  - clinicians providing care to target populations within the relevant specialty area, such as paediatricians or oncologists.
  - clinicians with broader therapeutic expertise, such as clinical pharmacology and clinical pharmacy, including specialist expertise in relevant sub-populations such as paediatrics or geriatrics.
- → diverse consumer and carer perspectives
- → clinical ethicist (where available, or someone with clinical ethics expertise) to assist with frameworks for decision-making in complex cases where the benefit:harm profile is unclear (to assist in weighing and balancing beneficence, non-maleficence, autonomy), or where the cost of treatment may have major implications for health services (population-level justice).

If an MTC or equivalent committee lacks the appropriate expertise to evaluate the off-label use of a medicine, it is recommended that appropriate external specialists or experts be invited to participate in the evaluation process.[44]

When considering off-label use for specific cohorts (for example, when seeking inclusion on a hospital formulary), seek advice from independent experts, namely, experienced clinicians who are not part of the local requesting team.

GUIDING PRINCIPLE 4

Involve the consumer in shared decision-making and obtain informed consent when recommending the use of a medicine off-label.

SHARED DECISION-MAKING

Shared decision-making is an important part of delivering **person-centred care** and is a collaborative process between consumers** and healthcare providers. It integrates the consumer's preferences, needs, values and goals with the best available evidence on the potential benefits, likelihood of harms and uncertainties of treatment.[45] Consumer focused, shared decision-making is also required within the **National Safety and Quality Health Service (NSQHS) Standards**.[46]

In addition to usual shared decision-making, consumers should be actively engaged in discussions about a medicine's off-label status including:

- → The reasons for considering the off-label use of the medicine.
- → The strength of evidence supporting its use.
- → Expected benefits, possible risks, and any uncertainties regarding these.[9]
- → Available alternatives (including on-label uses of medicines included in the ARTG).

** Note that, within this document, "consumer" includes both the person receiving care, their family and/or their carer(s).

- → Any access, affordability or practical treatment considerations, including (where relevant) financial consenting which outlines the likely cost and duration of treatment. This should also include costs of ongoing supply following any transitions of care, and in the community, and any limitations on how and where the medicine can be accessed.
- → Any conflicts of interest.

Open discussion of the above points is a fundamental legal, ethical, and professional obligation for all clinicians to obtain informed consent and plays a crucial role in delivering person-centred care. It is also an important liability consideration (see also **Guiding principle 8**).[47, 48]

Expert evaluation alone may overlook an individual's own treatment priorities, which can differ from clinicians' assumptions. Shared decision-making for patient-based benefit–risk assessment draws on the individual's lived experience, not only at the point of decision-making but also in shaping what level of risk they are willing to accept.[49] This is especially relevant when high-quality evidence is limited. Clinicians are responsible for individual-specific assessment that considers individual risk factors, comorbidities and the consumer's preferences/goals of care. This complements expert, evidence-based analysis, supporting enhanced consumer involvement, satisfaction, adherence and clinical outcomes.[49]

Considering the consumer's health literacy, developmental capacity, as well as their cultural and linguistic background is an essential component of the shared decision-making process. It is expected that clinicians discuss all information in a way that is appropriate to the consumer's needs. This includes provision of age-appropriate information for children and young people so that they can be meaningfully involved in decisions about their own care, to the extent that is appropriate for their own developing decision-making capacity.

For consumers whose first language is not English, using the support of credentialled interpreters is recommended when required (for example through **Translating and Interpreting Service (TIS)**) and other hospital or community-based services). For all consumers information should be provided using plain and accessible language, with written materials offered to support understanding and informed decision-making where appropriate. Note that the PI or Consumer Medicine Information leaflet will not include specific guidance on off-label use, so additional and more tailored information may be necessary.

Clinicians should also consider the individual's decision-making capacity and refer to their relevant state or territory health consent policies especially for those with reduced or developing capacity. Decision-making capacity is not binary but exists along a spectrum, and may fluctuate over time.[50, 51] Even where a substitute healthcare decision-maker is providing consent on behalf of a consumer, the consumer should still be involved in decisions about their care to the greatest extent possible, in a manner that is proportionate to their level of decision-making capacity at the time.[50]

The **CATAG Off-label Medicines Consumer Counselling Tool** supports shared decision-making with consumers enabling clear, accessible discussions about off-label use of medicines. More information can also be found regarding shared decision-making on the **Australian Commission on Safety and Quality in Health Care** website.

INFORMED CONSENT

Shared decision-making and informed consent are closely linked. Informed consent is a voluntary decision to proceed with a healthcare intervention by a consumer or substitute healthcare decision-maker after receiving accurate, balanced information and gaining a clear understanding of the expected benefits, risks and therapeutic alternatives.[45, 52] Informed consent should be obtained and documented whenever an intervention is offered, including the prescribing or use of a medicine off-label, except in emergency circumstances where immediate treatment is required. This supports a consumer's right to information as outlined in the **Australian Charter of Healthcare Rights**, and is a health professional's obligation under the relevant **Professional codes of conduct** and the **National Prescribing Competencies Framework**.[25, 53, 54]

> **Note:** In critical illness, affected individuals may have diminished capacity to consent to off-label use of a medicine.[55] While it is considered good practice for all clinicians to try to obtain consent from a substitute decision-maker, urgent treatment may proceed without consent when it will protect the individual's health or life.[56]

Documented consent should be communicated alongside other information relevant to the off-label use of the medicine, both across the medicines management pathway and at transitions of care (see **Guiding principle 5**).

For more information on informed consent, see the Australian Commission on Safety and Quality in Health Care's **informed consent fact sheet** for clinicians, which provides details on the key principles for informed consent and highlights the duty of clinicians to warn about material risks (including the benefits and risks of harm of alternatives and no treatment) or refer to your local guidelines.[57]

The strength and quality of evidence available to support off-label use, should guide the nature of the informed consent process and how consent is documented. This is described in Table 2.

Table 2: Informed consent requirements for off-label use of medicines

ROUTINE USE

Follow the usual process for consent as part of standard clinical care when the off-label use of a medicine is classified as routine use and there is high-quality evidence supporting such use.

Clinicians should discuss with the consumer that the use is off-label where this is clinically or financially relevant, is likely to be material to the consumer's decision-making, or if there is something known about the individual that would indicate they would attach some significance to the off-label aspect of their treatment. Documentation of this discussion and verbal consent in the medical record will often be adequate for routine off-label use however in some cases obtaining written informed consent may be judicious.

CONDITIONAL USE

When the medicine is being used off-label according to *pre-specified criteria for a select group of individuals*, clinicians initiating the treatment should **obtain written informed consent and document this alongside the rationale in the medical record**.

EXCEPTIONAL USE

When the use of the medicine off-label is considered exceptional use for a *specific individual*, **clinicians should obtain written informed consent and document this alongside the treatment rationale in the medical records**. Clinicians should provide a detailed discussion about these aspects with the consumer and/or carer and include information on the benefits and harms of the medicine and available alternatives.

Outside of routine use, detailed discussion is required with the individual and/or carer, about the off-label use of a medicine, including its potential benefits, risks of harm, and available alternatives. This type of use involves uncertainty and depends on careful, ongoing monitoring of effectiveness and safety. Consent should include for the necessary monitoring, which may represent increased obligations for the consumer regarding testing or clinic attendance.

For conditional and exceptional use categories of off-label use of medicines, collection and sharing of outcome data will contribute to the evidence base and support future decision-making. To do this, however, requires appropriate consenting and ethical approval. Clinicians should refer to their local HREC for advice. See also **Guiding principle 7**. Where information is collected **beyond routine care/use** the appropriate pathway for evaluation or research should be determined in accordance with local governance and ethics requirements prior to this data collection occurring.

RESEARCH USE

When an off-label use of a medicine is classified as investigational or experimental, use will be via a clinical trial and/or a HREC approved research protocol. It is important to explain, from an ethical standpoint, that prescribing this medicine requires it to be used within a research framework. It should be clearly distinguished that this constitutes research, rather than individualised clinical prescribing, even when it takes place in a clinical setting. **Written informed consent is essential** in this setting.

Requirements include an HREC-approved protocol treatment and the relevant information and consent forms used for gathering and documenting consumer consent.

↳ HOSPITAL SETTINGS

If a medicine has strong evidence to list it on the hospital formulary for an off-label use, then that use can be considered "routine use". In this case, the consenting requirements are no greater than for on-label use, however it is still considered best practice to include discussion of the treatment's off-label nature during normal consenting for treatment (as outlined above).

In this setting, any local governance processes should be followed.

Conditional use of medicines may also be incorporated into hospital formularies for specified population groups; in these cases, at a minimum, verbal consent should be obtained and documented.

FINANCIAL CONSENT

Off-label use of medicines may have financial implications for the individual's ongoing supply. Many medicines subsidised by the Australian Government through the Pharmaceutical Benefits Scheme (PBS) are limited to specific indications or populations as included in the ARTG. Therefore, use of medicines off-label requires an understanding and agreement between the consumer and the clinician as to how the medicine will be obtained. The person receiving care (or their family or carer) may therefore need to cover the full cost of the medicine when used off-label. Financial consenting in this setting is critical to minimise the risk of treatment failure due to affordability issues.

Other potential costs arising from uncertain efficacy and potential adverse effects may also need to be considered by the person receiving care and/or the health service when considering off-label use of a medicine.[13]

Pharmaceutical company subsided access through a Medication Access Program (MAP) or compassionate supply agreement may be available to reduce the cost of treatment. For more information on MAPs, please refer to CATAG's **Managing Medicines Access Programs: Guiding principles for the governance of Medicines Access Programs in Australian hospitals**.

In the public hospital setting, a clinician may be able to apply to the hospital MTC for hospital subsidised supply, however the treatment will likely be required to meet minimum evidence and cost-effectiveness thresholds for approval.

GUIDING PRINCIPLE 5

Provide and facilitate access to appropriate information regarding the off-label use of medicines at transitions of care.

These guiding principles outline requirements for documentation of several aspects related to the off-label use of medicines, including treatment rationale, informed consent and a detailed monitoring plan (See also **Guiding principle 6**). Outside of the "routine use" category for off-label use of a medicine (see **Guiding principle 2**) it may also be necessary to document how the evidence was identified and appraised, how uncertainty in the evidence was considered and how the evidence was weighed against other factors relevant to the decision-making.

All partners in the medicines management pathway, whether they are evaluating, prescribing, dispensing, administering or taking the medicine, require access to contemporaneous, accurate, timely, critically appraised and complete information to support safe and appropriate medicine use.[58] Therefore, regardless of the category of off-label use of a medicine, it is essential that complete information is available and transferrable across settings and supports safe, high-quality transitions of care.[58, 59]

Clinically meaningful and detailed information should be transmitted in a timely, bidirectional manner between and within primary care, hospitals, and aged care services, using available means such as, medical records, medicines reconciliation records, structured discharge summaries, shared access to My Health Record, clear annotation of

prescriptions and documented clinician-to-clinician communication where required. The prescriber or treating team initiating therapy off-label is generally responsible for communicating this information to support safe continuation or review of off-label use.

Communication should include:

- The indication for use
- Evidence supporting off-label use (including expected benefits and/or harms)
- Consent provided and by whom
- Dose, frequency and route of administration
- Administration instructions (including preparation instructions/formulation changes where relevant)
- Planned treatment duration and/or review timeframe
- Monitoring requirements (see **Guiding principle 6**)
- Criteria for earlier review or cessation
- Information to enable continued access (i.e. detail of the funding/access pathway).

Clear communication is especially important for any aspects of the medicine's use that are off-label. For example, if a higher dose or alternate route of administration is prescribed.

Hospital communications may include additional details such as the clinician or service responsible for ongoing management and monitoring of the off-label use of the medicine to enable easier communication.

Sharing this information supports person-centred care and QUM by enabling all partners in the person's care to review and monitor the off-label use for ongoing safety, effectiveness and appropriateness in alignment with QUM principles.[19, 24, 59] When the rationale for off-label use is unclear, clinicians (prescribers, pharmacists, nurses and other clinicians) should review available documentation (such as discharge summaries or correspondence from specialist clinicians) or seek clarification as needed. This supports continuity of care by confirming that off-label use is appropriate and safe.

Clear documentation also supports subsequent clinicians to continue the individual's care including ongoing reassessment of the benefit: harm profile as the individual's condition evolves and enables appropriate responses to any findings that fall outside expected parameters during monitoring.

GUIDING PRINCIPLE 6

Monitor and document the off-label use of medicines.

Off-label use of medicines should be subject to continuous monitoring of utilisation, clinical outcomes, and adverse events.[60] The scope and frequency of monitoring should reflect the individual's circumstances and category of off-label use.

Clinicians are responsible for prospectively establishing an appropriate monitoring plan at the time of initiating off-label use of a medicine. This plan should outline objective and clinically meaningful assessments for monitoring the safety and effectiveness of the medicine in the individual, with defined monitoring parameters, review timeframes and cessation triggers where relevant. Regular review is essential to mitigate the risk of continued use of treatments that are ineffective or unsafe. If the conditions for continued use are not met, or if new information indicates an unfavourable benefit: harm profile, then the medicine's use should be reviewed and likely discontinued.

The initiating clinician is responsible for documenting the planned monitoring and is then responsible for undertaking this monitoring or for clearly communicating monitoring requirements (as per **Guiding principle 5**) where care is transferred to another clinician.

Regular review of the individual is essential to mitigate the risk of continued use of treatments that are ineffective or unsafe,[28, 39] however, the nature and frequency of monitoring should remain subject to clinical judgement and evolving individual circumstances. Monitoring plans and clinical outcomes should be documented in existing clinical or institutional systems, and shared in a timely manner with other clinicians, especially at transitions of care (see also **Guiding principle 5**). This information should also be shared with the consumer and, where relevant, with the hospital's MTC.

Reporting adverse events to the TGA is important, especially for newly marketed medicines, new or unexpected adverse events, or where significant harm occurs. This applies equally to both on-label and off-label use of medicines. Consumers should also be advised of their ability to report adverse medicine events directly to the TGA (**www.tga.gov.au/safety/report-problem/report-adverse-event-or-safety-problem/reporting-adverse-events-consumers**) or via a healthcare professional.

Sponsors also have an obligation to report adverse effects for any medicine included in the ARTG, regardless of whether it is used for its approved indication or used off-label.[61] Reports on adverse events can be found on the **Database of Adverse Event Notifications (DAEN)**.

Table 3 outlines the monitoring requirements that should be followed when medicines are used off-label.

Table 3: Monitoring requirements for off-label use of medicines

ROUTINE USE

Monitoring requirements for 'routine' off-label use should follow the same principles as for on-label use of medicines. Additional monitoring requirements may be required in specific circumstances. For example:

- → assessing longer-term safety of a new medicine, particularly in special populations
- → monitoring to confirm alignment with anticipated expectations
- → monitoring of adverse events for high-risk medicines or vulnerable populations.

CONDITIONAL AND EXCEPTIONAL USE

Prospective evaluation of clinical outcomes, including safety and effectiveness, should be undertaken when using a medicine off-label within the conditional and exceptional use categories.

The treatment plan should clearly define outcome measures, follow-up timeframes and the use of both clinical data collected and consumer-reported information that will be collected during monitoring. Analysis should determine whether the results are clinically significant (for example whether benefits are observed and outweigh harms), along with documentation of any adverse effects and recommendations on the medicine's continued or future use.

RESEARCH USE

Ongoing monitoring and assessment of clinical outcomes for the off-label use of medicines should be undertaken and reported within appropriate timeframes, or as stipulated by the MTC. At an organisational level, monitoring of safety, efficacy, and other concerns associated with off-label use of medicines may be conducted for continuous quality improvement activities. Within hospitals, the MTC plays a key role in overseeing organisation-wide monitoring, particularly for conditional and exceptional off-label use. Where resources are limited, a risk-based approach may be used to prioritise medicines, clinical specialties, or populations that present the highest risk and require focused monitoring.

GUIDING PRINCIPLE 7

Evaluate the off-label use of medicines and disseminate the results and outcomes.

Formal evaluation of outcomes associated with off-label use of medicines may strengthen the evidence base, assist others in future treatment recommendations, and support collective learning. This approach supports clinicians in making informed decisions about the ongoing approval of off-label use of medicines and is consistent with general ethical principles.[62]

Data collected during the monitoring of off-label use of medicines can be useful to inform a structured evaluation of effectiveness and safety. This is especially important for conditional use situations.

Where there is a significant evidence gap, CATAG encourages the dissemination of outcomes through peer-reviewed publications and/or relevant registries. Especially 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. If considering publication, early advice should be sought from an institutional HREC so that these activities are conducted in accordance with ethical requirements.

Evaluations will benefit from support across the healthcare system (for example Primary Healthcare Networks, health services, aged care facilities and academia) to facilitate the design, conduct and analysis of robust studies reporting meaningful outcomes. Support may include access to data systems, study design, analytical expertise, and ethics advice where required enabling the systematic collection of clinically meaningful outcome data arising from off-label use of medicines.[63]

↳ PRIMARY CARE SETTINGS

In primary care settings, clinicians may wish to evaluate the off-label use of medicines as part of routine quality improvement and assurance activities. This could include reviewing the clinical rationale, evidence base, outcomes, and safety considerations associated with off-label use within their population group. Findings could be discussed within the clinical team to support shared learning, promote consistency, and reinforce safe, evidence-informed decision-making. Where appropriate, results may also inform local protocols or practice policies and contribute to broader organisational or network-level quality improvement initiatives.

↳ HOSPITAL SETTINGS

In hospital settings, where off-label use may have been approved by an MTC, outcomes should be reported to and evaluated by MTCs, as per the approval. Where outcomes will be shared beyond the MTC, HREC approval will often be required for this. The appropriate pathway for evaluation or research, including appropriate consumer consent, should be determined in accordance with local governance and ethics requirements.

GUIDING PRINCIPLE 8

Consider the legal and professional responsibilities relevant to off-label use of medicines.

Although medicines may be prescribed legally for off-label use,[8, 38, 64-68] this places an increased responsibility on the clinician to determine that such use is clinically justified, supported by appropriate evidence and consistent with accepted professional standards of care.[64, 69] Compared with on-label use, off-label medicine use may expose both the clinician and the health service to greater legal risk.

Given this increased risk, all clinicians should consult relevant educational resources, including this guidance and applicable legal, regulatory, and guidance frameworks, with direct reference to the relevant competencies of the **National Prescribing Competencies Framework**; competency area 4.3(a–c).[25] They should also review applicable professional standards and codes issued by their respective professional bodies or indemnity insurers and assess their professional indemnity arrangements if uncertain.

Although the prescriber holds primary responsibility for the prescribing decision, safe off-label use is a shared responsibility involving other clinicians and, where applicable, health service organisational governance. All clinicians are expected to exercise sound clinical judgement within their scope of practice and escalate concerns where the safety or appropriateness of prescribing is uncertain.[70]

Where the off-label use of a medicine evolves from conditional to routine practice, and is supported by high-quality clinical evidence, CATAG encourages sponsors to consider formal registration of the off-label use and clinicians to advocate for this transition. In alignment with principles of clinical governance and accountability, where sponsors engage in measures that support regulatory alignment, this will assist in addressing clinician uncertainty, reducing medico-legal indemnity concerns, and promoting the quality and safe use of the medicine.[71]

Off-label use should only occur where sufficient information is available to support use, and where the potential benefits and harms have been identified, evaluated and documented . Such use must be in the best interests of the person receiving care, both clinically and financially, and must comply with accepted standards of professional practice.[48] Where off-label use is widely accepted by the clinician's peers as constituting competent professional practice, and the individual has provided informed consent for its use, then off-label use should not, in itself, imply negligence in the event of harm. Clinicians following these guiding principles are more likely to meet their insurance, regulatory and other obligations.

While availability of profession specific guidance regarding off-label use of medicines is limited, all clinicians should consider their legal liability and professional accountability when prescribing, supplying and administering medicines off-label.

- Dispensing pharmacists have a professional obligation to confirm that medicines supplied are safe and appropriate and to understand the risks associated with supplying a medicine for an off-label indication, dose, route of administration or population group.[68, 72] Where concerns arise, pharmacists should contact the prescriber to discuss these issues.
- Nurses and midwives responsibilities, as outlined in the **Australian Nursing and Midwifery Federation's Quality use of medicines position statement**, remain directly relevant to the use of medicines off-label.[73] These include using evidence-based information to guide decisions, understanding the potential benefits and harms of medicines, and applying professional judgement to question the appropriateness of a prescribed medicine when necessary.

The obligation to inform consumers that medicines are being used in an off-label manner involves consideration from regulatory and civil liability perspectives and may vary according to individual circumstances. To support shared decision-making and informed consent (see **Guiding principle 4**), it is generally appropriate to advise the consumer explicitly that the medicine is being used off-label and explain what this means.[48]

FOR THE FUTURE

Drawing on input from CATAG and Expert Advisory Group members, along with consultation with external stakeholders, several key areas have been identified to inform future work to enhance quality use of medicines outcomes related to the off-label use of medicines. The areas outlined reflect those most consistently identified across stakeholder groups as important for development.

1. STRENGTHEN CAPABILITY THROUGH EDUCATION AND PRACTICAL SUPPORTS

Develop nationally consistent education and training resources to support health professionals in the quality use of medicines off-label.

- → Building capability in evidence appraisal and evidence-based decision-making.
- → Improving awareness of regulatory and access considerations.
- → Providing practical implementation tools (for example checklists, decision aids) to support off-label use in routine practice.

2. ENABLE NATIONALLY COORDINATED DATA, MONITORING AND EVIDENCE GENERATION

Progress a national approach to the systematic collection, linkage and use of data on off-label use of medicines.

- → Establish a national repository or registry for off-label use.
- → Define a minimum dataset to support monitoring, evaluation and pharmacovigilance.
- → Support timely generation and use of real-world evidence to inform practice and policy.
- → Provide open access to outcome data, where appropriate, to strengthen the evidence base for off-label use of medicines.

3. IMPROVE TRANSPARENCY AND CONSISTENCY IN DECISION-MAKING

Support greater clarity, consistency and visibility in how off-label use is considered across the health system.

- → Supporting consistent identification and communication of off-label use in medicines information sources, formularies and clinician communication.
- → Improving transparency of evidence underpinning formulary decisions.
- → Promoting more consistent approaches across jurisdictions to reduce unwarranted variation in access.
- → Coordinated or centralised approaches to evidence review and decision-making for selected off-label uses.
- → Targeted consideration of paediatric populations within policy and governance frameworks, recognising the routine and necessary use of off-label medicines in paediatric care and strengthening safeguards through robust approaches to risk assessment, evidence generation, and oversight, to address distinct vulnerabilities and counter the inadvertent normalisation of higher risk prescribing, particularly where off-label use is categorised as exceptional or research use.

GLOSSARY

Adverse event: An incident that results, or could have resulted, in harm to a consumer. A near miss is a type of adverse event.[74]

Clinician: A healthcare provider, trained as a health professional. Clinicians may provide care within a health service organisation as an employee, a contractor or a credentialed healthcare provider, or under other working arrangements. They include nurses, endorsed midwives, medical practitioners, nurse practitioners, pharmacists, allied health practitioners, technicians, scientists and other clinicians who provide health care, and students who provide health care under supervision.[46]

Consumer: A person who has used, or may potentially use, health services, or is a carer for an individual using health services.[74]

Cost-effectiveness: The degree to which something is effective, relative to its (typically financial) cost. This may be a comparative measure against other options, or a stand-alone assessment of whether an approach represents "good value".

Evidence-based: A term used to describe a practice, medicine use or information that is backed by scientific evidence. Evidence-based medicine, which extends to the evidence-based use of medicines, is described as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individuals.

Expert: an individual with a high level of knowledge, skill and experience in a particular field. "Expert" may refer to a person from a range of specialist areas and can include professional groups such as medical specialists, specialist General Practitioners, nurses, pharmacists or clinical ethicists.

Formulary: A resource that includes, but is not limited to, a list of medicines and medicine-associated products or devices, with approved indications or population groups for use. Formularies also typically include supporting resources such as medicine-use policies, important ancillary medicines information, and decision-support tools. Depending on the scope of the MTC that manages the formulary, the formulary may apply to an individual hospital, a hospital group, a geographical region, or an entire state/territory. Ideally, a formulary is a dynamic resource that is reviewed and updated regularly.

Health service: An organisation responsible for the clinical governance, administration and financial management of a health service unit(s) providing health care.[74] A health service may include one or many health service units, working across one or many physical locations (sites) within that organisation's governance.

Health technologies: Health technology is a broad term meaning something that is intended to do any of the following: prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; organise delivery of health care. Health technologies include tests, medical devices, medicines, vaccines, blood products, procedures, programs or systems involved in health care.

Informed consent: A person's voluntary decision about their health care that is made with knowledge and understanding of the benefits and risks of harm involved.[75]

Individual patient use/approval/application (IPU/IPA): A request to the MTC (or approval by the MTC) for an individual to use a non-formulary medicine or to use a medicine outside of its existing formulary approval.

Medication management: Practices used to manage the provision of medicines. Medication management has also been described as a cycle, pathway or system, which is complex and involves a number of different clinicians. The consumer is the central focus.

Medicines management pathway: The system used to manage the provision of medicines to consumers that are specific to a healthcare setting. These systems include dispensing, prescribing, storing, administering, manufacturing, compounding and monitoring the effects of medicines, as well as the rules, guidelines, decision-making and support tools, policies and procedures in place to direct the use of medicines.[76]

Medicine: A chemical substance given with the intention of preventing, diagnosing, curing, controlling or alleviating disease, or otherwise improving the physical or mental welfare of people.[77] Prescription, non-prescription and complementary medicines, irrespective of their administration route, are included.[74] Depending on the context, medicines may also be referred to as medication or pharmaceuticals.

Medicines and Therapeutics Committee (MTC): The group assigned responsibility for governance of the medication management system, and for the safe and effective use of medicines in the health service. MTCs may be responsible for medicines governance in a single hospital/facility, a local area health service, a healthcare network, or an entire state/territory. These committees may also be known by other names such as: Medicines Advisory Committee; Medication Management and Safety Committee; Drug and Therapeutics Advisory Committee, or Quality Use of Medicines Committee.[44]

Off-patent medicines: Medicines for which patent protection has expired, meaning the original sponsor no longer holds exclusive rights to manufacture or market the product.

On-label use of a medicine: Refers to prescribing and using a medicine exactly in accordance with the approved Product Information as authorised by the Therapeutic Goods Administration.

Person-centred care: Person-centred care recognises each individual as more than their medical condition, treating them with dignity and respect. Person-centred care is respectful of, and responsive to, the preferences, needs and values of patients, their family and carers. This approach involves collaborating with the patient and those around them to make shared decisions and set meaningful goals for care.[78] Also known as patient-centred care or consumer-centred care.[74]

Pharmaceutical Benefits Advisory Committee (PBAC): is an independent Australian expert body, appointed by the Australian Government, that recommends which medicines and vaccines should be listed on the Pharmaceutical Benefits Scheme (PBS). Members include doctors, health professionals, health economists and consumer representatives. PBAC evaluates the clinical effectiveness, safety, and cost effectiveness of

medicines to ensure Australians receive affordable access to treatments that provide value for public funds.[79]

Prescriber: for the context of this document a prescriber is a health professional who undertakes prescribing within their level of competence and scope, with the intent to initiate a medicine. A non-medical prescriber is a qualified healthcare professional who is not a doctor but has undertaken additional education and training to prescribe medicines within their scope of practice. This includes nurses, pharmacists, and some allied health practitioners, who are authorised to prescribe medicines in accordance with relevant legislation, guidelines, and their level of competency. Within this document "prescribe" and "prescriber" are used in relation to the decision to initiate a medicine. It is acknowledged that some health professionals will initiate treatment with a medicine without completing the legal act of prescribing (for example pharmacists recommending over-the-counter medicines). All clinicians initiating treatment with a medicine should consider these guiding principles and apply the recommendations for "prescribers" and "prescribing" when initiating a medicine, even without a written "prescription".

Primary care clinicians: Primary care clinicians (medical and non-medical) are health professionals who deliver first contact, accessible, and continuing care in the community. This group includes prescribers such as general practitioners, pharmacists, optometrists, endorsed midwifes, nurse practitioners and other allied health practitioners (both subject to State and Territory regulations), as well as community based pharmacists and nurses.

Primary care: Primary care is the first level of contact for individuals with health services and brings health care as close as possible to where people live and work. It is usually delivered outside hospital settings and provided within the community. It encompasses general practice, community health, aged care facilities, pharmacy, nursing, midwifery, allied health, mental health, oral health, and preventive services, and is delivered by a multidisciplinary workforce.

Quality improvement: The combined efforts of the workforce and others, including consumers and their families, researchers, planners and educators, to make changes that will lead to better health outcomes, better system performance (care) and better professional development.[80] Quality improvement activities may be undertaken in sequence, intermittently or continually.[46]

Quality use of medicines (QUM): The judicious, appropriate, safe and effective use of medicines.[19] This includes selecting treatment options wisely, choosing suitable medicines, and using medicines safely and effectively.[24]

Real-world data (RWD): Real-world data is data relating to individual's health status and/or the delivery of health care routinely collected from a variety of sources (for example data derived from electronic health records, medical claims data, pharmacy dispensing data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.[81]

Real-world evidence (RWE): Real-world evidence (RWE) refers to clinical evidence generated through the analysis of real-world data (RWD), providing insights into the use, benefits, and potential risks associated with a medical product or medicine.[81]

Risk assessment: A systematic process of identification, evaluation and estimation of the potential risks that may be involved in a situation.

Scope of clinical practice: the extent of an individual healthcare provider's approved clinical practice, based on the individual's skills, knowledge, professional registration (where applicable), performance and professional suitability and the needs and service capability of the organisation.[74]

Shared decision-making: Shared decision-making involves discussion and collaboration between a consumer and their healthcare provider. It is about bringing together the consumer's values, goals and preferences with the best available evidence about benefits, risks and uncertainties of treatment, to reach the most appropriate healthcare decisions for that person.[45]

Sponsor: The person or organisation responsible for a medicine's inclusion in the Australian Register of Therapeutic Goods (ARTG). The sponsor meets all regulatory obligations for that product, including supplying required evidence, maintaining compliance, and reporting adverse events to the Therapeutic Goods Administration (TGA).

Transitions of care: Situations when all or part of a consumer's care is transferred between healthcare locations, providers, or levels of care within the same location, as the consumer's conditions and care needs change.[58, 74]

Unapproved medicines: The term 'unapproved' in the regulatory context refers to medicines that have not been assessed by the TGA and are not included in the ARTG. In the international context this may be referred to as unlicensed. 'Unapproved' encompasses medicines that are:

- → not included in the ARTG and supplied under the Special Access Scheme or Authorised Prescriber Scheme
- → compounded by a registered pharmacist
- → used via our clinical trials exemption pathways
- → imported under the Personal Importation Scheme exemption.

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APPENDIX

Appendix 1
Evaluating the evidence for the off-label use of medicines

Appendix 2
How these Guiding Principles were developed

APPENDIX 1 - EVALUATING THE EVIDENCE FOR THE OFF-LABEL USE OF MEDICINES

To determine whether a medicine is suitable for off-label use, clinicians need to consider the strength of available evidence supporting that use. While reviewing evidence is a critical step in off-label prescribing decisions, it may not always require appraisal of primary literature. See also **Guiding principle 2**.

This appendix provides example resources and practical guidance for evaluating evidence in clinical practice, alongside useful tools to support critical appraisal of published literature and continuing professional development materials for clinicians wishing to further develop their skills in this area. Evidence-based medicine resources are presented in a hierarchical structure to support efficient evidence review starting with secondary sources such as high-quality treatment guidelines, followed by evaluation of the primary research literature.

In each case, the clinician needs to determine that there is adequate evidence to support the off-label use of a medicine, considering the benefits, harms, resource requirements and, where applicable, equity across the relevant population group. The threshold for "adequate evidence" to justify an off-label use may vary depending on the clinical seriousness of the condition being treated, such that lower levels of evidence may justify a trial of use when the condition itself poses a significant morbidity or mortality risk. Careful risk assessment will be required in each case of off-label use of a medicine, but this is especially critical where there is significant uncertainty in the evidence base.

EVIDENCE TO SUPPORT ROUTINE USE

EVIDENCE-BASED TREATMENT GUIDELINES

Where an off-label use of a medicine is supported within high-quality and up-to-date published treatment, international treatment guidelines or authoritative clinical references, the off-label use can be considered as routine use. It is justifiable for clinicians to regard off-label uses included in such guidelines, as being supported by adequately robust evidence of efficacy, effectiveness and safety and/or as representing established and accepted practice within the relevant medical condition. In these cases, no further evaluation of the evidence is required unless more contemporary evidence is expected in the primary literature or there is clinical reason to more critically appraise the available evidence (for example specific individual factors that may meaningfully alter the benefit-harm ratio).

See **Resources** for examples of national/international treatment guidelines and authoritative clinical references.

Evidence-based national and/or international guidelines often present treatment lines in a hierarchy, generally prioritised to present treatments with the strongest evidence of benefit as earlier/initial treatment lines. In most cases these treatment hierarchies can therefore be used as an indicator of comparative treatment benefits and strength of evidence to support use.

Clinicians using treatment guidelines to inform decisions about off-label use of a medicine should however apply caution as these secondary information sources have several limitations, especially for new medicines being used off-label. Treatment guidelines may focus primarily on efficacy evidence without adequate consideration or information about safety and/or cost-effectiveness, they may not provide useful information on comparative effectiveness, and the evidence used to inform the guideline recommendations may lack the quality and currency needed for robust assessment of off-label use.

IDENTIFICATION OF OFF-LABEL USE OF A MEDICINE

Treatment guidelines, evidence summaries and other medicine information sources do not always make a medicine's off-label status explicit. For example, the Australian Medicines Handbook uses the term "accepted indications" to describe uses that have not been approved by the TGA but where there is appropriate scientific evidence and/or broad clinical consensus to support their use.[32, 82] Many resources make no distinction at all between on-label and off-label uses of medicines in treatment recommendations.

To reduce ambiguity, CATAG recommends system-wide improvements to clearly flag uses as off-label at publication and, where possible, update this when regulatory status changes. Practical measures to increase awareness of a medicine's off-label use include flagging this in prescribing software, noting off-label status in formulary listings or clinical guidelines, and linking these to authoritative guidance on off-label prescribing. These measures should be supported by education to help clinicians both identify off-label uses and consistently apply the additional responsibilities associated with off-label use of medicines use (See also **Guiding principle 8**).

LEVEL 1 EVIDENCE

There is commonly a time lag between new evidence becoming available and subsequent inclusion in evidence-based treatment guidelines. Consequently, there may be strong, high-quality evidence for the off-label use of a medicine despite it not yet being included in published guidelines. Where there is valid, clinically meaningful and applicable level I evidence[29] to support the off-label use, this too can be considered routine use.

Level I evidence includes:

- → High-quality systematic reviews or meta-analyses of homogeneous randomised controlled trials
- → Large, high-quality, randomised controlled trials with narrow confidence intervals and low risk of error or bias.

See **Resources** for examples of level 1 evidence sources.

HOSPITAL SETTINGS: MEDICINE FORMULARIES

Off-label use of medicine may be included on a hospital or health service's formulary. In these cases, the responsibility for critically appraising the evidence rests partially with the committee that holds governance for the formulary, usually a Medicine and Therapeutics Committee (MTC) or equivalent. The formulary assessment process for an off-label use of a medicine should follow the same evaluation process as for on-label medicine assessments, however it may be necessary to search more widely for relevant evidence. Issues of equity may also be more significant when considering off-label uses, particularly where subsidised access to the treatment may not be broadly available. Refer also to the CATAG **Guiding Principles for Medicines and Therapeutics Committees in Australian Hospitals** for further information regarding the medicines governance roles of MTCs.

Within hospitals and other health services with a medicines formulary, where explicitly endorsed on the formulary, clinicians can be more confident that the off-label use has adequate evidence to support use. The clinician's responsibility regarding evaluation of the evidence is therefore primarily focused on considering the applicability of the evidence in the individual and, where relevant, considering comparative evidence for two or more treatment options.

Off-label uses that are classified as "routine use" will often be suitable for formulary listing if there is evidence to support cost-effectiveness.

Formulary listings may however apply conditions, such as previous lines of therapy that must be considered first, or defined outcomes for continued use of the medicine. i.e. off-label use of a medicine, even when formulary listed, may be a "conditional use". Clinicians will still therefore need to consider the strength and quality of evidence to support the formulary endorsed treatment when determining the appropriate safeguards around off-label use.

Note that hospital formularies can differ between each State and Territory and even between different hospital networks. Individual clinicians need to consult the relevant formulary for their work location.

Where an off-label use is not explicitly included on the health service's formulary, or for clinicians practicing in settings without a medicines formulary, the responsibility for evidence assessment rests with the prescribing clinician.

CONDITIONAL, EXCEPTIONAL AND RESEARCH USE

Where guideline recommendations and meta-analyses are not available to support an off-label use of a medicine use clinicians will need to critically evaluate the evidence themselves, noting that supports for this may be available in some settings (such as medicine information services or medical librarians).

Limited or low-quality evidence results in less certainty about the benefit, harm and cost-effectiveness of the medicine use. Consequently, the balance of benefits and harms may be less well understood,[13] highlighting the increased need for a careful risk-benefit analysis in these cases. In such cases with uncertainty in the evidence base, clinicians should adopt a more cautious approach to off-label prescribing, which includes consideration of other clinical management options such as other medicines or evidence-based non-pharmaceutical methods of management.

Off-label uses of medicines supported by only lower levels of evidence will generally require expert advice from the relevant speciality area. Even when an off-label use of a medicine is within an individual prescriber's scope of practice, it may be more practical, efficient or appropriate to refer to, or collaborate with, expert clinicians in the relevant area.

INTERDISCIPLINARY ASSESSMENT OF EVIDENCE

An appropriate mix of expertise is needed to best determine which evidence is appropriate for a given health issue or context and to assess its validity, clinical meaningfulness and applicability. This is particularly important where available evidence may be limited or uncertain (see **Guiding principle 3**).[28] An interdisciplinary approach is encouraged and, where available, off-label use that is supported by low to moderate or low level evidence should be considered only with the support of an MTC (either through a conditional formulary listing, or individual patient use approval).

Lower levels of evidence that may be used to support conditional, exceptional or research off-label use include (from stronger to weaker evidence):[29]

- → Individual randomised controlled trials
- → Pseudo-randomised controlled trials
- → Comparative studies with concurrent controls
  - Non-randomised experimental trials
  - Cohort studies
  - Case-control studies
- → Comparative studies without concurrent controls
  - Historical cohort studies
  - Two or more single arm studies
- → Case studies including case series
- → Expert opinion.

Although this list provides a hierarchical list, it will still be important to consider confounding factors, potential biases, and methodology flaws that may influence study outcomes. It is possible, for example, that more robust evidence could be provided by a well performed cohort study that accounts appropriately for confounding factors, as compared to a small randomised controlled trial with methodological flaws and/or a high risk of bias.

In some instances, high-quality research evidence may not yet be available. In the case of rare conditions or unique clinical circumstances high-quality evidence may be unlikely to ever become available. In the absence of high-quality evidence, recommendations from authoritative sources (for example medicines compendia, professional societies and colleges) that are supported by limited evidence and consensus opinion, may be appropriate for established uses of older medicines. Generally, however, when high-quality evidence is limited, critical appraisal of the primary research literature will be required, especially for newly marketed medicines or proposed new uses of older medicines.

REAL-WORLD EVIDENCE

Real-world evidence (RWE) may be gathered using a variety of research methodologies including cohort studies, case-control studies and case series. The value of RWE in enhancing regulatory and clinical insight is recognised internationally and nationally[63, 83] and it is used for ongoing evaluation of benefit: harm by medicines regulators such as the TGA.

High-quality RWE can help to address key limitations of clinical trials, especially the lack of evidence in under-represented populations such as obstetrics, paediatrics and geriatric populations. RWE is however susceptible to bias that can be difficult to detect, undermining credibility and complicating potential inclusion in decision-making.[84] As such, effective use of RWE in clinical decision-making requires relevant specialised methodological expertise to inform rigorous evaluations.

LITERATURE SEARCHING

Conducting a comprehensive literature search is a specialised skill. Clinicians who are not yet proficient should consider seeking support from medicines information services (including medical librarians) where available. When reviewing primary literature, it is important to undertake a thorough search using appropriate and well-constructed search terms, critically appraise the strength, quality, and potential biases and validity, clinical meaningfulness, and applicability of identified studies, and consider both positive and negative findings in the overall evidence assessment. It is essential that selective citation is avoided for transparency and balance.

While artificial intelligence (AI) tools will produce evidence summaries, clinicians are cautioned to declare any use of such tools and to carefully fact-check any AI generated evidence summaries. AI tools can produce incomplete, biased or inaccurate responses, so while they may be a useful support to clinicians, they cannot replace clinician literature searching and evidence review.

ACCESS TO INFORMATION

Access to high quality evidence is essential for sound decision-making. Clinicians require equitable and timely access to information and decision support tools to enable effective evaluation and guide appropriate use. However, research evidence is often restricted by journal paywalls, limiting access for clinicians without paid subscriptions or institutional affiliations.

Information from the pharmaceutical industry may be considered in evidence evaluations, including any unpublished data (including safety data) and additional information a company may hold on the use of a medicine.[44] However, industry-provided data should be scrutinised for completeness, potential conflicts of interest (both financial and non- financial)[85] or study biases that may be present with information from, or funded by, pharmaceutical companies.[44]

COMPARING EVIDENCE

Strength and quality of evidence need to be considered to determine the certainty regarding clinical trial findings. However, to compare different treatment options the magnitude of demonstrated benefit and/or harm also needs to be considered. For example, it may be more appropriate to select a therapy with moderate evidence that supports a significant clinical benefit, rather than another therapy with strong evidence of only a small, potentially clinically insignificant benefit.

When comparing evidence for different treatment options, clinicians also need to be conscious of possible confounding factors. For example, safety evaluations tend to be biased toward newly registered medicines over older medicines. This is primarily due to the limited safety data available at the time of registration compared to real-world evidence from long-term use of older medicines. Clinicians should also consider whether there is an efficacy-effectiveness gap, where medicines appear to work in the pivotal clinical trials but do not work as well in clinical practice.[86] Such limitations should be carefully considered when interpreting comparative safety and effectiveness data, as they may affect the reliability of claims of superiority for off-label use.

Additionally, clinicians should apply caution when comparing outcomes from different studies. Clinical superiority can only be demonstrated in a head-to-head trial, but often a head-to-head comparison will not be available to support decision-making between two potentially suitable treatment options. While examination of similar studies may give an indication of relative benefits and safety, differences in trial design, baseline characteristics of participants and outcome measure will confound such comparisons.

DOCUMENTATION OF EVIDENCE REVIEWS

Where evidence reviews are conducted to support off-label use of medicines these reviews should be documented to support:

- → expert review of the evidence (where relevant)
- → meaningful engagement with consumers
- → communication with other clinicians, especially at transitions of care
- → transparency over time, including in the context of future reviews for the same off-label use
- → medicines governance processes (such as consideration for formulary listing where applicable).

This documentation should include not only the findings of the evidence review but also detail on how relevant evidence was identified and appraised, and how any uncertainty in the evidence base was considered and managed.

RESOURCES

This section provides a selection of information sources, tools and continuing professional development (CPD) to support clinicians in further developing their skills in critical appraisal of the literature. Access to some resources may require a paid subscription. These lists are illustrative rather than exhaustive, and other relevant information sources and CPD opportunities are also available.

INFORMATION SOURCES

NATIONAL/INTERNATIONAL TREATMENT GUIDELINES AND AUTHORITATIVE CLINICAL REFERENCES

- *Therapeutic Guidelines*[87]
- *Australian Medicines Handbook*[32] (note that off-label indications are referred to as "accepted indications" in the AMH)
- National Health and Medical Research Council (NHMRC) Guidelines[88]
- Specialty specific national guidelines and resources such as AMH Children's Dosing Companion[89], AMH Aged Care Companion[90], EviQ Cancer Treatments Online[91]
- Specialty consensus statements published in peer-reviewed journals
- Specialty specific international guidelines such as the BNF for Children[92], National Comprehensive Cancer Network Guidelines[93], Maudsley Prescribing Guidelines in Psychiatry[94], **UK Palliative Care Formulary**[95]

EXAMPLE RESOURCES FOR CLINICIANS TO IDENTIFY LEVEL 1 EVIDENCE

- Collated meta-analysis or systematic review resources such as the **Cochrane Library**
- Primary literature can be searched (see below) for published systematic reviews or meta-analyses

PUBLISHED RESOURCES TO SUPPORT OFF-LABEL ADMINISTRATION

- Don't Rush to Crush[96]
- MIMS Disperse & Crush Guide[97]
- Australian Injectable Drugs Handbook[98]

REGULATORY OR HEALTH TECHNOLOGY ASSESSMENTS

Regulatory or health technology assessment decisions may provide an evidence overview and/or can aid in understanding the national and international regulatory context for the medicine.

- → TGA Australian Register of Therapeutic Goods (**ARTG**) and Australian Public Assessment Reports (**AusPAR**)
- → Pharmaceutical Benefits Advisory Committee (PBAC) **public summary documents**
- → National Institute for Health and Care Excellence (NICE) **Guidance**
- → New Zealand's Medicines and Medical Devices Safety Authority **MEDSAFE**
- → **Canada's Drug Agency** (formerly CADTH)
- → USA's Food and Drug Administration **Drugs@FDA**
- → **European Medicines Agency**
- → **Scottish Medicines Consortium**

PRIMARY LITERATURE

- → Primary literature can be searched using scholarly search engines such as **PubMed**, **Ovid** or **Google Scholar**

CRITICAL APPRAISAL TOOLS AND RESOURCES

Evidence-based medicine and critical appraisal articles:

- → **Critical appraisal: how to evaluate research for use in clinical practice**
- → **How to Read a Paper: The Basics of Evidence-Based Medicine**
- → **Evidence-based medicine: useful tools for decision making**

Users' Guides to the Medical Literature (JAMA Series):

- → **I. How to get started**
- → **II. How to Use an Article About Therapy or Prevention**
- → **IV. How to Use an Article About Harm**
- → **VI. How to Use an Overview**
- → **VIII. How to use clinical practice guidelines. Are the recommendations valid?**
- → **IX. A method for grading health care recommendations**
- → **XIV. Applicability of Clinical Trial Results**

OTHER TOOLS

- → **APPRAISE: A Tool for Appraising Potential for Bias in Real-World Evidence Studies on Medication Effectiveness or Safety**[84]
- → **REporting of studies Conducted using Observational Routinely collected health Data (RECORD)**[99]
- → **Critical appraisal checklists**

CONTINUING PROFESSIONAL DEVELOPMENT

NHMRC guidelines for guidelines

- → **Identifying the evidence**
- → **Synthesising evidence**
- → **Assessing risk of bias**
- → **Assessing certainty of evidence**
- → **Selecting studies and data**
- → **Evidence to decision**

Governance & Guideline Development Support:

- → **Achieving effective medicines governance: Guiding principles for Medicines and Therapeutics Committees in Australian hospitals**
- → **A new system for grading recommendations in evidence-based guidelines**
- → **The GRADE book** - Grading of Recommendations Assessment, Development and Evaluation

Training & Learning Modules:

- → **EBP Learning Modules 1–4 (Clinical Information Access Portal, CIAP)**
- → **Cochrane Interactive Learning** (some courses require subscription)
- → **Critical Appraisal Training online course** (fees apply)

APPENDIX 2 - HOW THESE GUIDING PRINCIPLES WERE DEVELOPED

These Guiding Principles provide an update to the 2013 CATAG document *Rethinking medicines decision-making for off-label use of medicines: Guiding Principles for the quality use of off-label medicines (Version 1)*. This updated document reflects the evidence available in 2025 and expands the scope to include private hospitals and primary care, with funding support from the Australian Commission on Safety and Quality in Health Care (ACSQHC).

The foundations of the Council of Australian Therapeutic Advisory Group's (CATAG) *Rethinking medicines decision-making for off-label use of medicines: Guiding Principles for the quality use of off-label medicines*, released in 2013, was built upon work initiated more than two decades earlier. In 2003, the NSW Therapeutic Advisory Group (NSW TAG) developed a consensus framework to support consistent, evidence-informed decision-making around off-label use of medicines in Australia.[20] This early framework provided practical guidance for prescribers and Drug and Therapeutics Committees (DTCs), now referred to as MTCs, in assessing the appropriateness of off-label use.

Variability in the use of decision-making frameworks across Australia and internationally, as well as in specific clinical areas such as paediatrics, led the Australian Health Minister's Advisory Council (AHMAC) Paediatric Pharmaceuticals Working Group in 2005 to highlight the need for national guidance on off-label use of medicines.[100] The World Health Organisation also commissioned guidance to help address this issue globally when developing the first Essential Medicines List for Children in 2007.[27] This was followed in 2010 by the National Medicines Policy Executive formally supporting CATAG's proposal for the development of a national approach to address off-label prescribing.[13] This led to CATAG's development of the national *Guiding Principles for the quality use of off-label medicines*.

Since 2013, a range of national organisations have supported and recommended their use to guide the safe, transparent, and evidence-informed use of medicines off-label.[††]

Alongside a review of the literature, eleven qualitative interviews were conducted with representatives from primary care and MTCs across Australia. These then informed the update of these Guiding Principles.

CATAG convened an Expert Advisory Group (EAG) to review the *Version 1* of the Guiding Principles and advise on changes. The EAG was comprised of individuals with recognised expertise in a range of areas, such as clinical practice (medical, pharmacy, nursing), evidence-based medicine use, clinical ethics, consumers, medicines information developers, TGA, medicines governance and MTC operations. All comments provided by the EAG were discussed and considered for incorporation into these Guiding Principles. Input on the document was also sought from the ACSQHC.

The EAG met on three occasions via video conference, with emailed discussions and document review between meetings. The EAG provided endorsement of the final draft document on 22nd June 2026.

External stakeholder consultation was undertaken in April 2026. CATAG member organisations and 48 external stakeholder organisations were invited to provide feedback on the drafted document. Responses were received from representatives of 25 organisations, including public and private hospitals, state and territory health departments, and national professional organisations.

These Guiding Principles were developed in consultation with and endorsed by representatives from the CATAG member organisations on 30 June 2026. See **catag.org.au/organisations** for details and contacts.

[††] Faculty of Pain Medicine Australian and New Zealand College of Anaesthetists. Off-label prescribing in pain medicine practice: Overview. 2024.

- The Royal Australian and New Zealand College of Psychiatrists. Professional Practice Guideline 4: 'Off-label' prescribing in psychiatry. Melbourne RANZCP; 2023
- Australian Medical Association. Position statement on Medicines 2021. AMA; 2021.
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT). Royal Australasian College of Physicians (RACP) "Evolve": Recommendations, 2024 [Available from: **www.racp.edu.au/evolve/recommendations/australasian-society-of-clinical-and-experimental-pharmacologists-and-toxicologists**].

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