ACE CLINICAL GUIDANCES
METHODS AND PROCESSES MANUAL

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ACE
agency for
care effectiveness

Record of updates

Date	Version	Summary of main changes
May 2025	1.0	Publication of the ACE Clinical Guidances Methods and Processes Manual.

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Foreword

Established by the Ministry of Health (MOH), the Agency for Care Effectiveness (ACE) is the national health technology assessment and clinical guidance agency in Singapore. We develop and publish clinical guidelines that provide concise, evidence-based recommendations to inform specific areas of clinical practice. These national-level guidelines are referred to as ACE Clinical Guidances (ACGs) and serve as a common starting point for clinical decision-making. Find out more about ACE at www.ace-hta.gov.sg/about

The ACE's Methods and Processes Manual for ACG Development (hereon referred to as the Manual) outlines the core methodology underpinning ACGs, including topic identification/prioritisation, guideline scoping, evidence identification and assessment, formulating clinical recommendations, stakeholder consultation, and process for updating.

This Manual intends to standardise and document the methods that ACE follows for ACG development, and to increase transparency of our processes and recommendation-making frameworks. It is not a comprehensive academic or technical document. Alongside ACE staff, the Manual supports the appointed Expert Groups members when advising on the development of an ACG. However, they are not bound to adhere to it in every detail, or in every case. Information in this document may also be useful for:

- Healthcare professionals who want to better understand methods that underpin the ACG recommendations and contents
- Other guideline developers who want to apply ACE's methods for developing guidelines or who need a reference resource when planning their own guideline development process
- Policy makers who want to be familiar with how ACG recommendations are developed for informing implementation plans or needs

This Manual describes the methodology specific to ACGs, which follows a hybrid adaptation and de-novo process. Guideline developers applying different methods can refer to the "Guidelines for Guidelines (G4G)" – a set of minimum standard practices to maximise the trustworthiness of guideline recommendations, regardless of whether de-novo, adaptation, or adoption methods are used.

ACE will continue to review and update this Manual to ensure it remains a useful resource for the Singapore healthcare system.

ACE would like to thank the following experts for their advice and contributions to the development of the ACE's Methods and Processes Manual version 1.0 for ACG development (appointments listed were current when the Manual was first published in May 2025):

- Professor Zachary Munn (Director, Health Evidence Synthesis, Recommendations and Impact (HESRI), School of Public Health, The University of Adelaide; Director, JBI Adelaide GRADE Centre; Past-Chair, Guidelines International Network (GIN))
- Practice Guidelines Committee under the Office of Professional Affairs, Academy of Medicine, Singapore
- Associate Professor Edwin Chan (Director, Cochrane Singapore; Associate Professor, Duke-NUS Medical School; Chief Scientific Officer, Singapore Clinical Research Institute)

1. Introduction

Clinical guidelines are important knowledge tools that summarise evidence and present recommendations to support clinical decision-making. The demand for evidence-based, national level clinical guidelines continues to grow as keeping abreast of new publications represents a major challenge for healthcare professionals due to the exponential growth in the number of publications. Clinical guidelines have a range of purposes, from improving effectiveness and quality of care, to decreasing unnecessary variations in practice and decreasing costly preventable mistakes and adverse events. However, their potential benefits are only as good as the quality of the guidelines themselves. Trustworthy clinical guidelines are "…the cornerstone of giving evidence-informed advice in response to clinical, public health and health policy questions. They address those questions by using the best available evidence and transparently integrating the judgements of experts and the input of stakeholders in the process" (WHO Handbook for guideline contextualization, 2023). The main objective of clinical guidelines is to improve the quality of healthcare by closing the gap between current and best practices.

The Evidence to Practice Office (ETPO) in ACE develops ACE Clinical Guidances (ACGs), which carefully balance evidence-based best practices and local feasibility considerations – to provide a set of clinical recommendations tailored to Singapore's context. All published ACGs can be found on ACE Clinical Guidances (ACGs) (ace-hta.gov.sg). Following publication, ETPO also engages key stakeholders to facilitate adoption of the ACG recommendations through various implementation strategies.

ETPO employs a rigorous and systematic process for the development of ACGs, as summarised in Figure 1 below.

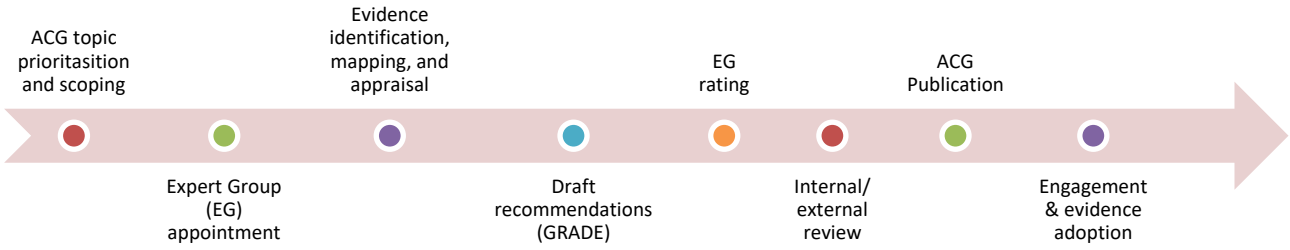

Figure 1. Overview of ACG development steps

The Manual's subsequent chapters provide a detailed description of each of the above steps, including the roles and responsibilities of key players: (i) the Evidence to Practice Advisory Committee (ETPAC) for topic prioritisation; (ii) ETPO for overall technical (evidence) work; and (iii) the appointed Expert Groups (EGs) for clinical inputs.

2. Topic selection for ACG development

The topic selection process decides which disease areas should be ranked and prioritised for ACG development by the Evidence to Practice Advisory Committee (ETPAC)[1], chaired by Director-General of Health (DGH). The process has been designed to ensure that chosen topics address clear local care gaps and that a clinical guideline can address barriers contributing to the identified gaps, ultimately supporting healthcare professionals to provide appropriate care. Topics are identified annually and consists of (i) a public call for ACG topics, (ii) an internal horizon scan, and (iii) a review of existing ACGs that are due for updating (see section 'Updating the ACG'). Off-cycle ad-hoc ACG requests may be considered depending on the clinical need, importance, and urgency.

ETPO collates all topics for that year through the above-mentioned approaches and conducts a rapid situation analysis to assess suitability for ACG development. Topic summaries are prepared and circulated to ETPAC. Key information for each topic includes:

- Disease burden (prevalence, incidence)
- Impact on health (state, morbidity, mortality)
- Healthcare utilisation & cost
- Appraisal of local & key international guidelines
- Current practice & potential gaps
- Relevant cost-effectiveness evidence where available.

ETPAC ranks the topics based on the following principles:

- Importance to health: impact on health outcomes and healthcare utilisation
- Potential impact: likelihood that a clinical guidance (ACG) could address clinical issues, practice gaps, unwarranted variation in care delivery, or low-value care
- Opportunity for change: feasibility of incorporating the ACG recommendations into clinical practice, having considered the infrastructure readiness and effort required
- Appropriateness in practice: urgency (importance and need) to address the clinical issues or practice gaps

Highest-ranked topics are prioritised for ACG development and approved as part of the ETPO's workplan. Based on ETPAC's discussion and advice, lower-ranked topics could be considered for collaboration with other local guideline centres/teams, re-considered for topic prioritisation the following year, or identified as not needing a guideline (for example, if other interventions may be more appropriate).

[1] ETPAC composition, chaired by DGH, includes the following representatives: relevant MOH policy or services divisions, public healthcare institutions, private primary care, Health Promotion Board, Master of Academy of Medicine Singapore, and Dean of NUS Saw Swee Hock School of Public Health. ETPAC's terms of reference are in Annex 1.

3. Scoping

Building on the findings developed to inform ETPAC's prioritisation exercise, ETPO conducts formative research to guide the scope of each ACG:

- An iterative, mixed-method approach is employed to contextualise the clinical issues to the local context by reviewing local literature and analysing epidemiological data, knowledge-attitudes- practices (KAPs), or process-related data.
- Available quantitative data is coupled with survey responses from healthcare professionals and/or focus group discussions/in-depth interviews with relevant stakeholders.
- The above findings are triangulated to help describe the clinical condition and practice, define key local gaps and identify the potential barriers and facilitators for practice change.
- Best efforts are made to identify other relevant MOH initiatives, services or healthcare policies and programmes in the topic space. This enables the establishment of the ACG's role within the larger ecosystem of interventions and minimises duplication of efforts. It also serves to liaise with key policy owners (if available) who can be better served to implement or incorporate the ACG recommendations after publication.

The ACG's objective, areas to be covered, and target audience are defined based on these findings – with inputs and adjustments from the appointed Expert Group (EG) during the early ACG development phase.

4. Appointing an Expert Group (EG)

A multidisciplinary EG is appointed for each ACG to ensure that clinical content is accurate, current, and relevant for local practice and intended users. The EG terms of reference are in Annex 2. EGs play a key advisory role throughout guideline development, and their inputs are specifically sought for:

- Refining the scope, target audience, and setting that the ACG aims to focus on
- Agreeing on the clinical questions to match the scope of the ACG and on the review questions to be addressed by the in-house systematic reviews
- Advising on systematic review protocols (PICO)
- Rating the appropriateness of draft recommendations, as based on GRADE factors
- Reviewing the full ACG draft for clinical accuracy

Besides clinical evidence, EGs are required to consider ACG implementation needs, such as the feasibility of implementing the recommendations (including likely costs/savings for the healthcare system), factors that may help or hinder implementation ('levers and barriers'), and implementation support that may be required beyond ACG dissemination. To meet the above, the EG needs to be multidisciplinary and representative of views from all relevant clinical settings or practices. Typically, they consist of practising public and private sector healthcare professionals, who are subject matter experts, and can include specialists, general practitioners, pharmacists, allied health, and nurses, as appropriate. See 'Process for identification of EG members' for more details.

Usually, two co-chairs are appointed to lead the EG by facilitating effective and open discussions, and moderating deliberations concerning the development of the ACG. Co-chairs are selected from

specialties or settings that require greater emphasis in perspective. For example, for ACGs providing guidance to doctors in the primary care sector, one co-chair will be identified from family medicine physicians. Co-chairs are appointed based on considerations such as sufficient seniority, experience with facilitating large group discussions, and ability to deliberate on evidence-to-decision considerations from a national perspective. The exact composition of each EG is tailored to the guideline topic and is approved by the DGH. All EG members have equal status, acknowledging the importance of the expertise and experience that each member brings. Depending on the topic, ETPO may co-opt experts into the ACG development process. These experts are invited to contribute to a specific part of the guideline only. They may take part fully in discussions or only provide written inputs, but they do not have voting rights or count towards quorum.

4.1 Declaration of interests and safeguard of official information

Declaring and managing conflicts of interests (COIs) are fundamental to maintaining public trust and protecting organisational integrity.

Prior to appointment, all nominated EG co-chairs and members are required to declare to ETPO any direct or indirect interest that could potentially be perceived to influence the issues under consideration by the EG. Once appointed, any new interests or changes to existing interests must be disclosed to ETPO during the ACG development and/or before each meeting. Each appointed EG member is also asked to sign the Undertaking to Safeguard Official Information.

While COIs do not in themselves imply improper motivation or wrongdoing, early identification and management of conflicts could prevent more serious issues from developing and ensures objective decision-making in crafting the guideline recommendations. Referencing established international standards, ACE is moving towards a standardised approach to obtaining COI declarations; assessing and evaluating; and taking steps to manage COIs (direct or indirect) appropriately to reduce the risk of bias. This may include implementation of controls depending on the nature of the COI and the role played by the individual in the committee/group.

5. ACG development

The ACG development process involves the technical (evidence) team from ETPO, and a clinical panel which comprises the appointed expert group (EG). ETPO provides the in-house expertise necessary for carrying out the technical aspects of the process which includes evidence synthesis, assessment of certainty, formulation of structured recommendations using the GRADE framework, and adherence to best practice methods for guideline development. In parallel, the EG, made up of multidisciplinary healthcare professional experts and other stakeholders, provides the contextual and clinical insights needed to ensure that the recommendations are relevant, practical, and grounded in real-world expertise. This ETPO-EG collaboration helps to ensure that our guidelines are both methodologically robust and clinically meaningful. The following subsections describe the roles and responsibilities of both groups.

5.1 Preparing relevant clinical questions

At the start of ACG development, ETPO formulates clinical questions (CQs) to match the scope of interest. CQs are broad in nature. Some examples are:

CQ	What is the recommended first-line treatment for <disease area>?
CQ	What are the diagnostic criteria for <disease area>?
CQ	How should patients with <condition> be monitored and followed up?

The CQs aim to break down the overall scope into more specific sections and to guide the identification of evidence. Clinical questions are then categorised based on whether they are expected to result in a recommendation or will inform clinical content in the supporting text of a recommendation. Usually, clinical questions are categorised as potential recommendations if they aim to address the "what" of clinical practices: for example, what treatment strategy to use, what assessment factors to consider etc. Supporting text to recommendations aims to address the "how" or more generally to provide information on putting the said recommendation to practice: for example, dosing/titration information, adverse effects, frequencies of review, application to patient subgroups etc. Deviation from this approach is possible, depending on the need and justification for it, and in consultation with the Expert Group.

5.2 Identifying the evidence

5.2.1 Clinical guidelines

An evidence search starts from existing, relevant clinical guidelines. Based on the scope, ETPO carries out systematic searches in guideline databases[2] using related medical subject headings, free-text terms and publication type filters where appropriate. Database searches are complemented by manual retrieval of guidelines published by relevant specialty associations from North America, Europe,

[2] Databases searched: The Guideline Central©, GIN Library, ECRI Guidelines Trust®, PubMed, Epistemonikos, Trip Medical Databases.

Australia, and Southeast Asian countries. English language guidelines published within the previous five years, and that address the scope of interest (hence, maximising the match between drafted CQs and international guidelines' recommendations), are prioritised for methodological assessment. If initial search yield is low, the search can be widened to include the previous 10 years. Conversely, if the yield of relevant guidelines is high, then priority may be given to those using a de-novo methodology (i.e. conducting original systematic reviews for all questions).

Two independent reviewers from the ETPO team assess the prioritised guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE-II) tool[3], *Domain 3. Rigour of Development*. Scaled domain scores are calculated and any significant difference is resolved by involving a third reviewer, if needed. A higher scaled domain score indicates higher methodological quality of the guidelines: ETPO applies a minimum of 60% scaled domain score for selection, unless there are other compelling reasons to include a guideline below this threshold. The guidelines selected at the end of this process become 'reference guidelines'.

5.2.2 Existing systematic reviews and meta-analyses

Even recent guidelines may not always present the most up-to-date evidence, due to a lag between systematic searches and guideline publication. For this reason, pooled data is identified from recent PubMed-indexed systematic reviews (SR), meta-analyses (MA) and network meta-analyses (NMA), to complement the information from high-quality guidelines.

5.3 Evidence mapping to answer clinical questions

Recommendations from the selected high-quality guidelines are mapped by ETPO against the CQs. A pre-determined template is used to extract each guideline recommendations against the CQs, level and quality of the evidence used by the guidelines, the guideline panel's judgement and evidence-to-recommendation justification (if available). Through this step, in-depth knowledge is built on the bases for international recommendations which inform our initial judgement on next steps required, including whether:

- Further evidence work is needed, for example in the form of an in-house systematic review
- Clinician inputs should be sought to clarify applicability of the evidence
- Studies conducted in local population or local data should be reviewed

5.4 Prioritisation and development of ETPO-led systematic reviews

Usually, most CQs can be answered based on the high-quality guidelines and SR/MA/NMA identified, with a sufficient degree of certainty. This evidence base then enters the evidence-to-recommendation framework for drafting recommendations (see 'Formulating draft recommendations' below). However, when CQs require further evidence work, an in-house systematic review is then triggered. Examples of when ETPO performs in-house systematic reviews to support ACG development include:

[3] AGREE Next Steps Consortium (2017). The AGREE II Instrument [Electronic Version]. From http://www.agreetrust.org.

- Suboptimal transparency from guidelines on evidence used and no recent SR/MA/NMA available
- No significant variation across guideline recommendations, but more recent studies suggest a change in the evidence base

If an in-house systematic review of the clinical evidence is prioritised, ETPO applies the following steps in accordance with established methods for systematic reviews:

- Formulate a clear review question
- Populate the review protocol (see Annex 3)
- Develop a reproducible search strategy (as a minimum, the following databases are searched: PubMed, Embase, WHO ICTRP; topic-specific databases are searched as appropriate, for example PsycINFO for mental health topics)
- Select relevant studies from title and abstract screening, and subsequently from full-text screening
- Extract studies data and assess risk of bias with predetermined checklists (e.g. Cochrane's RoB 2 or ROBINS-I tools)
- Assess the need and feasibility of meta-analysing effect estimates
- Assess certainty of the evidence by outcome using GRADE and produce summary of findings tables

The EG is required to agree on (i) the need to conduct an in-house systematic review, and (ii) the details of the review protocol (including the ranking of outcomes importance and definitions, see Annex 3).

5.5 Economic evidence

Guideline recommendations should consider the balance between the estimated costs of interventions or services and their expected benefits compared to alternatives (i.e. cost-effectiveness). Assessing the cost-effectiveness of an intervention or service helps to optimise the use of limited resources.

The process of defining the incorporation of economic analysis, including its form, begins during the scoping of the ACG and continues through the development of recommendations. Initially, a literature review is conducted to assess whether the scope's key questions have been addressed by existing studies on cost-effectiveness. If the available economic evidence is insufficient or inconclusive, the use of economic modelling approaches such as cost-utility analysis, cost-minimisation analysis or cost-impact analysis may be considered.

The incorporation of economic analysis into ACG development is relatively new and is currently being piloted. More details will be added in future iterations of this Manual.

5.6 Formulating ACG recommendations

5.6.1 Evidence to recommendation framework[4]

The totality of evidence available (from guidelines, existing SR/MA/NMA, in-house SR, or relevant economic evidence) enters a pre-defined evidence-to-recommendation (EtR) framework that guides the drafting of each recommendation. ETPO's EtR for ACG development is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, whereby the following four factors influence the direction and strength of recommendations:

1. **Balance of health benefits and risks** (trade-offs of desirable and undesirable outcomes), taking into account critical vs. important outcomes as discussed by the EG
2. **Certainty in the best estimates and magnitude of effects** (quality of evidence)
3. **Stakeholders' values and preferences, and their variability** (e.g. patient acceptability)
4. **Resource impact and feasibility considerations** (e.g. accessibility, cost, and implementation factors – including at the health system level)

More details to the GRADE approach can be found here guidelinedevelopment.org/handbook. Assessment of the four factors above guides ETPO in articulating and weighting key considerations, and how these led to the draft recommendation.

The strength of each recommendation is reflected by the verb used (ACG recommendations tend to start with an action and are not statements of facts). For example:

Recommendation strength and direction	Examples of verbs used
Strong (for)	Prescribe, use, add, offer, advise, provide access to, should
Strong (against)	Do not, avoid
Weak or conditional	Consider

As per the GRADE approach, a strong recommendation is usually made when benefits clearly outweigh the risks, based on at least moderate-certainty evidence. A weak or conditional recommendation may be needed when there is a closer balance between benefits and harms, evidence is of low certainty, or there is significant variability in patients' values and preferences.

In the absence of direct empirical evidence, ACGs allow for recommendations to still be made, where needed and justified. In such instances, other literature sources are referenced (e.g. indirect evidence/data, high-quality international guidelines recommendations etc) and the clinical need for a recommendation is clearly stated. Where no significant concerns are identified on other EtR domains, the strength of the recommendation is deliberated upon by the EG and can result in a 'strong for/against' recommendation. ACGs do not differentiate between recommendations and good practice statements/good practice points (no labelling is applied), to simplify the readers'

[4] Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook.

understanding of action required. Nevertheless, a full EtR is published alongside each ACG so that the underpinning factors (including possible lack of direct evidence) and justifications leading to the strength of each recommendation are summarised.

The above considerations and related draft recommendations are collated into an 'EtR document' which is then surfaced to the EG for appropriateness rating (see section 'EG rating of appropriateness' below).

The strength of recommendations has different implications for different users. Some examples are provided below:

ACG user	Strong recommendation	Conditional recommendation
Healthcare professional	Most patients should receive this clinical practice.	Shared decision-making may be especially relevant, as the decision to apply the recommendation could largely depend on practical or patient-specific considerations.
Policy maker	There is greater certainty for adopting the recommended practice as part of health policies.	It is less likely that the recommended practice can be adopted for national-level health policies as is, and additional judgement is required if considered.
Patient	Most individuals would want to receive the recommended course of action and only a small proportion would not.	There may be greater variability in individual preferences and values, with shared decision-making playing an especially relevant role.

5.7 EG rating of appropriateness

The draft recommendations and their underpinning EtR prepared by ETPO are circulated to the EG for their input. EG members are requested to individually **rate the appropriateness** of the draft recommendations. In doing so, they are asked to consider the GRADE factors informing our EtR framework (see section 'Evidence to Recommendation framework' above) and to refer to the following definition of 'appropriateness':

> In summary, **a recommendation can be considered appropriate if there is confidence that the benefits of a specific practice outweigh the risks. It also implies that most or all patients would be best served by the recommended practice.**[b]

Informed by the above considerations, the EG rates the appropriateness of each recommendation **on a scale of 1 (inappropriate) to 9 (appropriate)** by answering the question: **How appropriate is it to recommend this practice to this extent/strength?**

For example:

Recommendation A: Consider offering [intervention X] to all patients.

Recommendation B: Ensure all patients receive [intervention X].

In both recommendations, the practice (i.e. patients receiving Intervention X) is the same. However, depending on how the statement is worded, the rating may not be the same because it also needs to take into account the extent/strength (i.e. 'Consider offering' vs 'Ensure') of the recommendation.

The above approach to deliberation and rating is based on the RAND/UCLA Appropriateness Method (RAM), which is a modified Delphi method:

a. The EG's ratings are done individually; responses are blind to each other and, are submitted back to ETPO.
b. Internally, the team assesses the level of agreement on the appropriateness of recommendations, by using the two statistical measures developed by RAND/UCLA: the interpercentile range (IPR) and interpercentile range adjusted for symmetry (IPRAS)[5]. In addition, ETPO adds two more layers of assessment: (i) coefficient of variation: there is no validated cut-off determining agreement; simply, the larger the coefficient of variation, the greater the variance in ratings; (ii) visual inspection of ratings dispersion on the 1-9 scale.
c. Besides numerical ratings, the EG can include qualitative feedback, supported by at least one peer-reviewed article if a change to the recommendation is proposed.
d. Based on these considerations, ETPO reviews the recommendations and identifies areas where rating dispersion/ variation warrants specific discussions with the EG (often regardless of whether agreement was reached).
e. Their individual scores are sent back to them and shown against the median EG scores for each recommendation.
f. A meeting is scheduled for discussing areas identified through steps a-d and the EG conducts a second round of rating for the revised recommendations. This iterative process continues until there is a convergence of opinion but typically, this is achieved after the 2nd round of ratings. Nevertheless, further meetings can be arranged depending on the complexity and extent of the discussion required.

[5] IPR is a commonly used statistical measure of dispersion of a distribution (i.e., in this case, how dispersed the ratings for a given recommendation are on a scale of 1 to 9). IPRAS was developed in addition to IPR to detect disagreement in the case of asymmetric ratings. Asymmetry is defined as the distance between the central point of the IPR and the central point of the 1-9 scale, i.e. 5. The more asymmetric the ratings are, the larger is the IPR required to say that there is disagreement. As each recommendation has its own internal symmetry, a different IPRAS needs to be calculated for each recommendation to detect disagreement (no universal cut-off is possible). Thus, disagreement with a given recommendation is defined if IPR > IPRAS.

More details to the RAND/UCLA method and process can be found here:
https://www.rand.org/pubs/monograph_reports/MR1269.html

5.8 Patient involvement

It is increasingly recognised and established internationally that the involvement of people with lived experience (PWLEs) in clinical guideline development is necessary for several reasons: it allows for practical insights in care delivery that healthcare professionals may not otherwise consider; their participation help better reflect patient preferences and values, so that the guidelines may more likely be accepted and followed; PWLEs' inputs can help highlight important quality-of-life considerations; and, it supports shared decision making between clinicians and patients.

Notwithstanding, ETPO acknowledges that there is a need to mitigate inherent challenges such as identifying balanced and diverse representation across different population groups, and bridging knowledge gaps and potential power imbalances between experts and patients. As such, the introduction of PWLE voice in guideline development will occur in phases, starting in 2025 to test out our pilot methodology, including purposive sampling for diversity and structured processes for meaningful engagement. Based on learnings from the pilot, we would refine our patient involvement methodology accordingly in subsequent ACG topics.

5.9 Drafting the full ACG

While recommendations are crafted as actionable statements, they may not be sufficient on their own to fully inform decision making. Full ACG writing is an essential step in ETPO's process to ensure that the appropriate context, additional considerations, clinical examples, or useful tools are presented in the guideline to support its use in practice. Clarity and user-friendly features are key to the ACG style. Where possible and appropriate, ETPO develops infographics, tables, mnemonics, or algorithms to convey complex information in ways that can be quickly assimilated by the user.

The writing process is iterative, usually involving 2 to 3 rounds of review by the EG. Edits are incorporated based on ACE's style guide for scientific writing, with inputs from a professional medical writer and a designer. Tools or derivative products of the ACG (such as patient factsheets and medications tables) are explored in the early phases of the ACG development and developed alongside the ACG writing.

6. External review

Once the EG and ETPO have finalised the ACG draft (including design elements) and its supporting EtR, external stakeholders are contacted for their review and feedback. At a minimum, the documents are circulated to the Academy of Medicine Singapore (AMS) and the College of Family Physicians, Singapore (CFPS) for their comments and endorsement. In keeping with international standards, reviewers from AMS and CFPS should have not been involved in the development of the ACG (e.g. they should not be part of the EG). Other reviewers are included in this process as needed, based on the topic and scope of the ACG. For example, ETPO might contact existing clinical workgroups under MOH, local specialty associations, or relevant policy divisions for comments. All comments are collated and responses prepared. Changes to the ACG are made where appropriate. Upon receiving endorsement from AMS and CFPS, their logos are appended on the ACG's front page.

When this process is concluded, the EG is requested to formally endorse the final ACG and its EtR via email; this is so that their names and affiliations can be added to the published guideline. As a last step, ETPO will seek approval from the DGH for publication and dissemination.

7. Publication and dissemination

Following DGH's approval, the ACG is published on the ACE website. The publication includes a web-based summary of recommendations, the full PDF guidance and pertinent references, the underpinning EtR, a list of related ACGs with links, and a list of other relevant resources (where applicable/available) – such as collateral clinician materials or patient-facing factsheets. These additional resources can be developed internally by ACE or be part of existing materials assessed to be suitable. The ACG is thereafter disseminated electronically to all registered doctors in Singapore via an electronic direct mailer (depending on the ACG topic and scope, electronic dissemination is expanded to pharmacists, nurses, and other healthcare professionals). Further dissemination and promotion activities are conducted through several channels. These include relevant websites (e.g. AMS, Primary Care Pages, public healthcare institutions' intranets), email networks, social media, and publications (e.g. College Mirror, SMA News, ACE Insights newsletters).

8. ACG implementation

While clinical guidelines can be appropriate evidence-based tools for improving patient outcomes, an active implementation strategy involving clinical champions is often necessary to encourage uptake. Recognising this, ETPO works closely with stakeholders including key organisations, healthcare professionals (especially the EG), and policymakers to facilitate the adoption of ACGs, taking into account system-, clinician-, and patient-level barriers and enablers. Besides targeted dissemination strategies (see section 'Publication and dissemination'), ETPO develops topic-specific implementation strategies to increase knowledge transfer, such as clinicians resources, webinars and academic detailing. Moving forward, efforts will be made to (i) strengthen implementation planning through behavioural insights and implementation science frameworks, facilitating more systematic mapping to identified barriers and enablers, and (ii) co-develop and customise implementation strategies that support evidence-based adoption with stakeholders and consumers. ACG implementation via clinical decision support tools will also be explored.

9. Updating the ACG

The full development of an ACG takes approximately 9 to 12 months. ACGs are usually reviewed around five years after publication, or earlier if new evidence emerges that requires substantive changes to the recommendations. Around the 5-year mark, ETPO assesses the extent of changes required for updating an ACG. If changes are deemed significant, the ACG enters the topic prioritisation process for that year (see section 'Topic selection for ACG development'). Minor changes, such as updating medications lists, are dealt with in addition to the agreed workplan for the year.

Certain significant recommendations (for example, recommendations underpinned by rapidly evolving evidence) are monitored more frequently, with yearly assessments of changes in the evidence or local context. In line with current best practices in guideline development and maintenance, a set of pre-defined 'triggers' determine when changes to ACG recommendations are warranted. These are:

- Change in international guidelines' position due to new evidence
- Change in the certainty of evidence
- Change in benefit-harm balance (e.g. change in magnitude or direction of treatment effects or new evidence on previously unknown harms of recommended treatment)
- Change in relative cost and availability of medications that warrant a change to recommended practice

EG's inputs are sought yearly on the above triggers for specific recommendations. Based on insights received, ETPO assesses the new evidence further to determine whether a change in a recommendation is required. If so, any revised recommendation with underpinning rationale for change is surfaced to the EG for appropriateness rating (see section 'EG rating of appropriateness'). The aforementioned approach was crafted after a 12-month pilot for maintaining "living" ACG recommendations for type 2 diabetes mellitus (T2DM); even with fast evolving evidence in the T2DM space, the efforts required for quarterly surveillance were disproportionate to the benefits gained – with no changes to the ACG recommendations. As a fit-for-purpose and feasible approach to maintaining up-to-date recommendations remains a priority for ETPO's processes, "living" ACG modalities will be reassessed should the need arise.

When an ACG is deemed unsafe to remain published (for example, direct misalignment with newer policies or safety concerns due to outdated evidence), it is retired from the ACE website.

10. Next steps

As ACE's strategy and capabilities evolve, so will the ETPO's ACG methods and processes. The following areas are currently being explored or piloted, and may be included in this Manual once our methods are consolidated:

- Involving people with lived experiences in the ACG development process (e.g. patients, carers, or patient advocates)
- Guideline implementation strategies, including development of clinical quality indicators and use of computable recommendations
- Evaluation of ACG adoption and or/impact

Annex 1. ETPAC's TORs

1. To prioritise and approve topics with the greatest potential for impact in evidence-based practice and appropriate care, for development into clinical guidances
2. To advise on opportunities for guidance implementation, and to facilitate collaboration with stakeholders to support ETPO's activities
3. To review high-signature ACG recommendations[6] based on factors such as, the clinical- and cost-effectiveness of ACE-evaluated health technologies, the clinical need, and estimated budgetary impact of such interventions.
4. To act as ambassadors to promote the adoption of guidance recommendations into clinical practice

Annex 2. ACG Expert Group's TORs

1. *[For Co-Chairs only]* To lead the Expert Group by facilitating effective and open discussions, and by moderating deliberations concerning the development and adoption of the ACG.

2. To support the development of the ACG by:
    1. Reviewing international/local guidelines and the evidence underpinning the ACG; and
    2. Advising on the relevance of the ACG for local practice; and
    3. Participating in meetings and email discussions related to the ACG; and
    4. Ensuring the accuracy, currency and applicability of the ACG by providing timely inputs, and incorporating appropriate and value-based care principles where needed; and
    5. Contributing to the development or refinement of resources accompanying the ACG, such as:
        - Developing content for practice support tools (e.g. medication tables, clinical algorithms, referral guides)
        - Providing feedback on patient education aids

3. To be an ACG adoption champion by applying ACG recommendations as appropriate in own clinical practice and to drive ACG adoption among peers via relevant initiatives, such as:
    1. Presenting ACG recommendations at relevant events or platforms (e.g. department meetings, teaching sessions, CMEs)

[6] Criteria for high-signature ACGs: the ACG topic and/or recommendations contained within are potentially sensitive or contentious; and, the recommendation(s) contained within the ACG are supported by ACE-conducted HTA and CEA; and, the recommendation(s) concerns a condition potentially eligible for subsidised treatment, but the accrued evidence suggests clinical inferiority to prevailing standard treatments and/or not found to be cost-effective; and, the above criteria notwithstanding, referral to the Committee remains subject to DGH's guidance and approval, following ACE's assessment and input from the relevant Expert Group and professional organisations where necessary.

2. Integrating ACG recommendations into institutional/practice clinical protocols, care pathways and clinical decision support tools
3. Identifying and addressing adoption barriers and enablers where possible

4. To support ACE in the assessment of the ACG impact, for example by sharing information as needed on:
    1. ACG adoption progress and uptake rates
    2. Clinical impact and outcomes
    3. Sustainability considerations

5. To support ACG outreach and awareness by:
    1. Disseminating ACG and related resources through institutional, professional networks and communication channels;
    2. Sharing ACG-related updates and resources on social media platforms e.g. LinkedIn, Facebook; and
    3. Facilitating connections between ACE and relevant professional networks or subject matter experts when needed; and
    4. Identifying opportunities for broader ACG dissemination, including internationally.

Annex 3. Example of PICO protocol

Adapted from NICE UK review protocol template

Review question	[State the question(s) to be addressed by the review, clearly and precisely.]
Objective	[Identify the objective of the review and how this is expected to add to what is already known.]
Condition or domain being studied	[Provide a short description of the disease, condition or healthcare domain being studied e.g. How should autism be defined/diagnosed?]
Population	[Include summary criteria for the participants or populations being studied by the review. For example, children and or adults (including age ranges), line of treatment, previous treatment, severity of condition.] Exclusion: [if applicable, provide exclusion criteria for the participants or populations being studied by the review.]
Intervention/Exposure/Test	[Supply full and clear descriptions or definitions of the interventions or the exposures to be reviewed. This is particularly important for reviews of complex interventions (those involving the interaction of several elements). If appropriate, an operational definition describing the content and delivery of the intervention should be given.]
Comparator/Reference standard/Confounding factors	[Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group), reference standard or confounding factors. Control or comparison interventions, reference standard or confounding factors should be described in as much detail as the intervention being reviewed. If the comparator is 'treatment as usual' or 'standard care', this should be described, with attention being paid to whether it is 'standard care' at the time that an eligible study was done, or at the time the review is done.]
Primary outcomes (critical outcomes)	[Outline the pre-specified primary (most important) outcomes / critical outcomes of the review, including details of how the outcome is defined and measured (such as validated tools or scales), when these measurements are made and follow-up, if these are part of the review inclusion criteria.] [please provide definition of outcome "improvement" – i.e. what constitutes clinical difference]
Secondary outcomes (important outcomes)	[List the pre-specified secondary (additional) outcomes / important outcomes of the review, with a similar level of detail to that required for primary outcomes.]
Analysis of subgroups	[Outline details of any subgroup that you would want to have evidence synthesis done for separately: patient characteristics (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or comorbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).]
Search strategy	[Provide details of search strategy, including databases searched, search strings, or terms used].

The Agency for Care Effectiveness was established by the Ministry of Health Singapore to drive better decision-making in healthcare through health technology assessment, clinical guidance, and education.

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