

# NCG

## Guidelines Manual 2021



# **NCG Guidelines Manual 2021**

Release Date November 2021  
Published by National Cancer Grid, Mumbai, India

## **Imprint for the NCG Guideline Manual**

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Release Date – November 2021

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## **Acknowledgements**

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## Preface

Clinical guidelines are *“statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and risks of alternative care options”*. However, the benefits of clinical guidelines can translate into improvement in quality of care only if they have been rigorously developed, and are feasible and applicable in the real world. This cannot be overemphasized in a country like India with vast variation in resources, infrastructure and expertise. Other important aspects are the process followed during the guideline development, addressing conflicts of interest, and their acceptability by health care professionals and other stakeholders. India being a hub of many diversified healthcare models, the National Cancer Grid (NCG) has developed guidelines for management of cancers with due consideration to all these factors which add complexity to optimal healthcare delivery.

As planned during the first edition, the second edition of the NCG guidelines are now available as resource stratified guidelines. This version makes “essential”, “optimal” and “optional” recommendations for management of cancers. This stratification allows healthcare providers to deliver the best possible care with the available resources, while ensuring value for the care provided.

The NCG guideline manual is a step towards streamlining the process of guideline development and subsequent revisions. The manual is developed by experts from the NCG collaborating with the Centre for Global Development after several rounds of discussion and deliberations. The manual is based on international standards for guideline development and the adaptation methodologies contextualized to the Indian setting. The manual will allow users and stakeholders to understand the process used in developing recommendations and methods used in reaching consensus decisions. The manual highlights the efforts which are underway to evaluate cost-effectiveness and will further promote value-based care in a country with several competing needs in healthcare.

We acknowledge the need for continuous evaluation of emerging evidence in cancer care as well as improvements in the guideline adaptation process. Timely revisions in coming years will continue to incorporate the best available evidence to guide cancer care in our country with the overall objective of eliminating disparities.

## Chapter 1. Introduction/purpose of the manual

### 1.1. Clinical guidelines

Clinical guidelines can be defined as: “Statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and risks of alternative care options”<sup>1</sup>.

Clinical guidelines are crucial towards delivering safe, appropriate and efficient care, improve patients outcomes and ensuring an optimal and effective use of healthcare resources<sup>2</sup>. They form an important part of the quality improvement and provide systematic and transparent methods by which providers can deliver evidence-based practice<sup>3</sup>.

Clinical guidelines can also help in ensuring that patients are informed about what clinicians should be doing, the benefits and risks of treatment options and the services they can expect, including enhancing the doctor-patient relationship<sup>4</sup>. Clinical guidelines also help improve efficiency and optimize value for money, thus benefiting providers, receivers and payers.

Importantly, clinical guidelines are regarded as key levers to help improve quality of care, itself a cornerstone of Universal Health Coverage (UHC). UHC is defined as “ensuring that all people have access to the health services they need, when and where they need them, without financial hardship. It includes the full range of essential health services, from health promotion to prevention, treatment, rehabilitation, and palliative care”<sup>5</sup> [https://www.who.int/healthsystems/universal\\_health\\_coverage/en/](https://www.who.int/healthsystems/universal_health_coverage/en/) (accessed 22 February 2021). India has made important progress towards UHC with the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (AB-PMJAY) Programme launched in 2018. Clinical guidelines are seen as instrumental in informing the Health Benefits Packages and their implementation throughout India.

However, clinical guidelines can only bring these benefits if they have been rigorously developed, seem feasible and reasonably applicable and if clinicians are aware of their existence and agree to incorporate these into their clinical practice. This requires an effective communication, identifying barriers to change and specific implementation interventions. The key stakeholders, including patients should be involved and consulted with in the process of clinical guideline development. Likewise the dissemination and implementation of clinical guidelines should be carefully planned and transparent in order to achieve a successful change in clinical practice<sup>6</sup>.

### 1.2. The National Cancer Grid (NCG)

The National Cancer Grid (NCG) is a network of over two hundred major cancer centres, research institutes, patient groups and charitable institutions across India, covering 60% of cancer care in India. Its mandate is to establish uniform standards of patient care for prevention, diagnosis, and treatment of cancer, providing specialized training and education in oncology and facilitating collaborative basic, translational and clinical research in cancer. It is an initiative of the Government of India, led through the Department of Atomic Energy and its grant-in-aid institution, the Tata Memorial Centre.

### **1.3. The NCG guidelines**

The clinical guidelines developed by the NCG aim to improve the quality of clinical cancer care in India. They are equally relevant to public and private cancer providers: all clinicians, managers, payers (health insurers), and also to patients. Linking to the Ayushman Bharat-PMJAY scheme, the NCG clinical guidelines aim towards strengthening delivery of cancer services under AB – PMJAY by providing guidance to standardize and optimize beneficiaries' care and to support better decision-making during disease management and reimbursements for improved patient outcomes

The NCG guidelines can be used to develop quality standards for measuring and assessing the clinical practice of cancer care, to educate and train cancer providers and to improve communication and shared decision-making between healthcare providers and patients.

The NCG guidelines are based on the best available international and local evidence, and are a ready resource to guide the cancer care delivery by hospitals and research centres which are a part of the NCG. They are developed using recognised methods that are sound and transparent and take account of the views of stakeholders (healthcare providers, patients, health service managers, health insurers and other stakeholders) through a consultative process. The guidelines are available at: <https://tmc.gov.in/ncg/>

The methodologies detailed in this document relate specifically to the development of high quality cancer clinical guidelines. However, the development principles and templates could be applied to other diseases as well, in order to set optimal /benchmarks standards for clinical practice in India.

### **1.4. What is the purpose of this manual**

The main purpose of this manual is to guide developers of the NCG guidelines in their work to ensure that guidelines meet international standards of quality<sup>7</sup>. These guidelines address all aspects of cancer management, including diagnosis, treatment and palliative care. The manual will also help users of the NCG guidelines and relevant stakeholders understand the provenance of the recommendations and how the decisions were reached.

This manual draws on accepted international standards to guideline development and nascent adaptation methodologies contextualised to the Indian setting. It takes into account approaches reported in guidelines manual of major international and national programmes, including WHO<sup>8</sup>, the National Institute for Care Excellence (NICE)<sup>9</sup>, the Institute of Medicine<sup>10</sup> and established national cancer programmes<sup>11</sup>. It also reflects the current state of development in the field of guideline development and adaptation<sup>12, 13</sup>. Using existing cancer guidelines is central to NCG guideline development, but NCG guidelines are designed specifically for India and require contextualization to be relevant to the Indian setting (see Chapter 4). It should be noted that methods for adapting guidelines are dynamically evolving and are likely to change in the future as new evidence emerges.

The development of the NCG guidelines is evolving. The NCG guidelines developed until now have followed a process that was commensurate with the technical and logistical resources available on the ground. This has relied mostly on the clinical expertise of experienced cancer experts from the NCG centres, on their knowledge of research and evidence in the field of

oncology. Given the increasing demands for clinical guidelines in India, and requests from the recent AB-PMJAY scheme the NCG guidelines will require additional resources to support the clinical experts and provide the necessary technical capacity.

Whilst this manual takes into account the current methods of NCG guideline development it aims to provide guidance for an expanded and systematised NCG guideline development process that is of international standards and yet is achievable and appropriate for India.\

### **1.5. Updating the NCG guideline manual**

This manual will be updated every 3 years after publication. However, in case significant changes to the process of guideline development and adaptation occur during that period, the manual will be edited in accordance to ensure it follows the latest international standards of guideline development.

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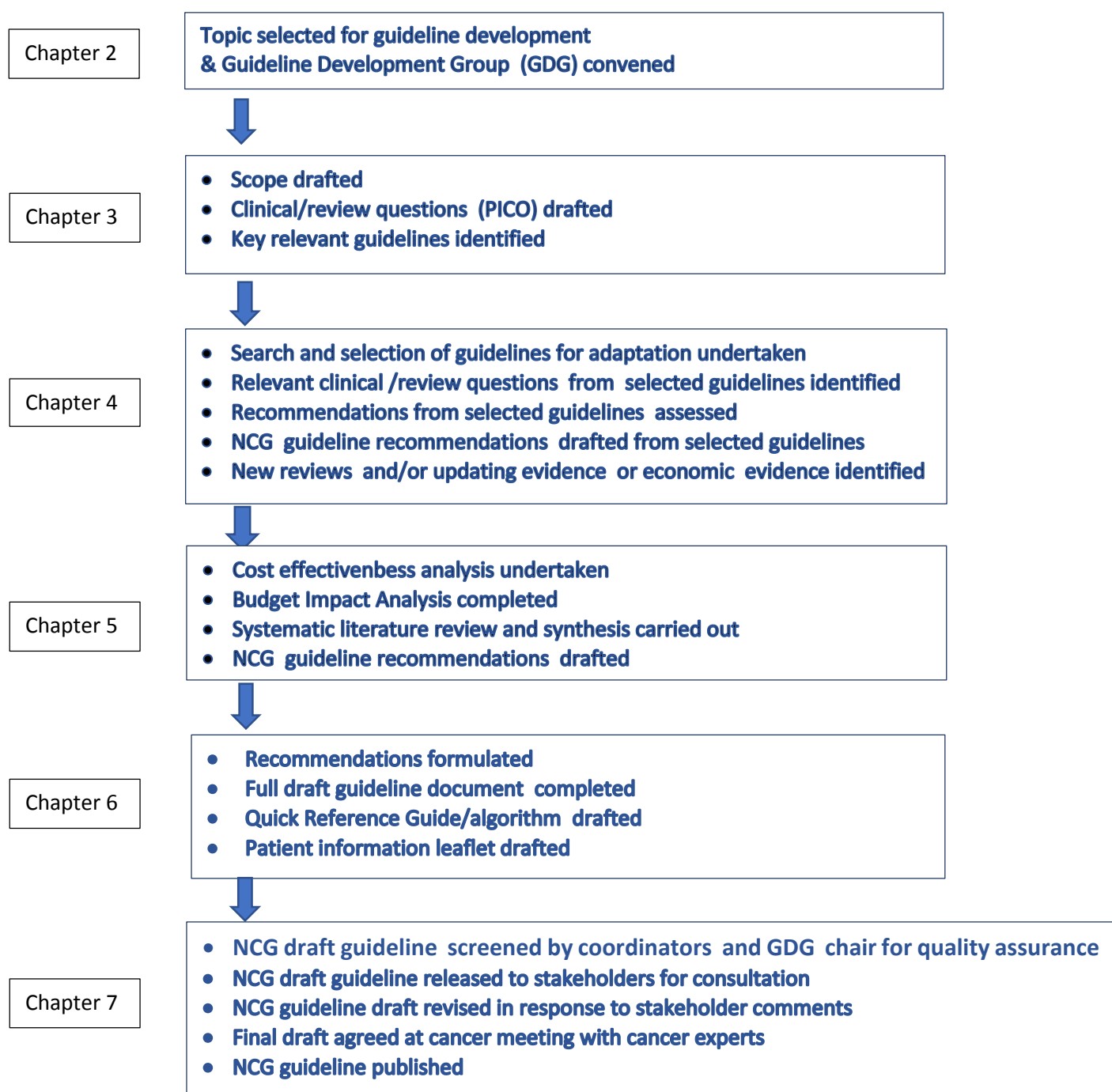
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## Chapter 2. Who develops the NCG clinical guidelines

### 2.1. The NCG guidelines development process overview

The NCG guidelines are developed through a systematic process of technical planning, evidence reviews and discussions led by cancer experts with inputs from relevant stakeholder groups and patients (see relevant chapters). The development and review of NCG guideline is a continuous process. Figure 1 outlines stages of the development process.

**Figure 1. Overview of the NCG guidelines development process**



## 2.2. The Guideline Development Group (GDG)

The NCG clinical guidelines are developed by clinical cancer experts from the NCG organised as “Guideline Development groups “(GDGs) that include a fair regional representation. Each of these groups is responsible for specific cancer guidelines (for example, urological malignancies, head and neck cancer etc..).

Each GDG has a chair and two coordinators: one from the Tata Memorial Centre (TMC), the other from the NCG centres. Both coordinators provide the communication, logistics and coordination with the other experts on the GDG.

The GDG is involved throughout the development of the clinical guidelines. It drafts the scope and clinical/review questions, understanding the key clinical issues which need to be addressed in the guideline. The GDG then examines existing guidelines developed according to international guideline development criteria that are relevant (See Chapter 3). It determines whether any recommendations from existing guidelines can be adopted or need adapting to the Indian context. It also determines whether new clinical/review questions are needed in case key clinical issues relevant to India are not covered in the existing guidelines, including economic analyses (Chapter 4). If new (de novo) reviews are required, the GDG develop clinical/ review questions, assess the evidence and makes the recommendations according to international standards (Chapter 5).

At least two-thirds of GDG members should be present to finalize the guidelines (either a virtual or face to face meeting). The concurrence of the members can be obtained through email, in case such meeting is not feasible. The same needs to be documented in the guidelines document.

### 2.2.1. Forming the GDG

The Chair and members of the GDG are enlisted for the duration of a specific guideline development. One member of the GDG is elected as the Chair. The membership of the GDG should be multidisciplinary<sup>1,2</sup>. The exact composition of the GDG will be tailored to the topic covered by the guideline, reflecting the range of stakeholders and groups whose professional activities or care will be covered by the guideline. It should include technical and administrative /co-ordinating support staff and ideally at least one patient or patient advocacy /support group member who has experience or knowledge of issues related to patients and their families.

The GDG should ideally consist of 8 to 12 members<sup>3</sup>. Smaller groups may introduce bias or not have the full expertise required. Larger groups may reduce the effectiveness of group processes<sup>4,5</sup>. Evidence suggests that problems can arise when there are more than 15 members<sup>6</sup>. These risks can be reduced through diverse membership and effective chairing of meetings<sup>7</sup>. This balances the opportunity for individuals to contribute effectively with the need for a broad range of experience and knowledge. Members of the GDG should have sufficient expertise and credibility to command the respect of people within their field. The GDG has four key constituents:

1. **The NCG/TMC Chair**
2. **Specialists on Other healthcare professionals the topic:** This includes oncologists, surgeons, nurses, palliative care experts, and other health



## Chapter 2. Who develops the NCG clinical guidelines

professionals allied to medicine (e.g. pharmacists, rehabilitation therapists and others whenever feasible and relevant). Representation from both public and private sector is recommended.

3. **Two co-ordinators.** One from TMC another from NCG with technical knowledge on appraisal of evidence and evidence-based clinical guidelines.
4. **Patients.** These may be enrolled through patients' groups. This can be a patient or someone from a relevant patient support group. The GDG should have at least one patient/patient representative but it can have more patients /patient representative depending on the topic of the guideline. The patient representatives will be given a briefing regarding the role prior to enrolment in GDG.

Ideally, GDG members should be drawn from different parts of India but this will be influenced by the expertise available.

For some guideline topics, it might be important for the GDG to include other types of experts (for example, an epidemiologist, researcher, economist with specialist knowledge or clinical experts with specific clinical expertise): These experts advisers would help in the following ways:

- refine and agree upon the clinical/review questions to be addressed by the evidence reviews (for example, when topic-specific input is needed to further define outcomes or specify appropriate comparators) as defined in the scope
- advise on developing the review protocol and alternative analyses (Chapter 5)
- assess the current evidence and feasibility
- develop the recommendations
- consider the potential costs and savings with implementing the recommendations
- highlight factors that may help or hinder implementation ('levers and barriers')

### *Note on experts advisers:*

The expert advisers are not full members of the GDG; they do not have voting rights, and they should not be involved in the final decisions or influence the wording of the final recommendations. They should submit a declaration of interests form before attending the GDG meeting.

Other stakeholders, for example, representatives from hospital administration and/ or insurers may comment on the draft guideline during consultation (see Chapter 7). Manufacturers of pharmaceutical products or medical devices are not represented on the GDG because of potential conflicts of interest but may contribute as stakeholders during consultation.

All GDG members should be committed to developing the NCG guidelines according to the processes set out in this manual. They should attend all GDG meetings or calls and new members should not usually be added. People are GDG members in their own right, and do not represent any particular organization or Committee.

The roles of the GDG members are outlined below.

### 2.2.2 Role of the GDG chair

To work well, the GDG needs an effective chair. The chair guides the working group through the tasks (developing the guideline) and process, helping the group to work collaboratively, ensuring a balanced contribution from all members (see box 2.1 below). The chair may be a specialist in the guideline topic, but this is not essential because specialist knowledge can be provided by other GDG members .

#### Box 2.1. Key roles and responsibilities of the GDG Chair

- Leads the development of the guideline scope with the coordinators or technical team
- Has good knowledge of the skills mix available in the GDG
- Assist the NCG coordinators in drafting the full NCG guidelines report (See Chapter 6)
- Assist the NCG coordinators in screening the draft guideline for quality assurance (see Chapter 7)

**To facilitate the working of the GDG, the Chair has the following responsibilities:**

- Sets up the rules for how the GDG operates, based on the principles set out in this manual
- Plans and organizes the GDG meetings with the coordinators from NCG/TMC, including setting the agenda
- With the coordinators , ensures that GDG members have signed the declaration of interest form and handles any conflicts as they arise, in line with the policy (see section 2.3.)
- Establishes a climate of trust and mutual respect among members
- Provides opportunities for all members to contribute equally to the discussions and activities of the group
- May meet individual GDG members outside GDG meetings

**At the GDG meetings, the Chair:**

- Steers the discussions according to the agenda
- Keeps the group discussion unified and avoids disruption by sub-conversations or dominance by any members
- Encourages constructive debate, without forcing agreement
- Summarizes the main points and key decisions from the discussions
- Signs off meeting minutes once approved by the GDG.

The Chair approves the final full guideline report and the quick reference guide and patient information leaflet (See Chapter 6).

### 2.2.3. Role of Clinical GDG members

Clinical members of the GDG are on the group as healthcare professionals with appropriate knowledge and skills in cancer care; detailed research expertise is not necessary but an understanding of evidence-based medicine is required. They are not expected to represent the views of their professional organizations.

The roles and responsibilities of the clinical and other healthcare professional members of the GDG are shown in Box 2.2 below. The technical aspect of the development (searching, reviewing/assessing the evidence ) may be undertaken by some members of the GDG or by technical experts in systematic reviewing. In the former case GDG members should have received training on systematic reviews or health technology assessment, and on the process of guideline development. For health economics analyses the group may call upon health economists with experience in conducting such analyses.

*Note:* At present the NCG guidelines do not have methodologists or health economists. These roles may be undertaken by clinicians until the time when methodologists and health economists can be recruited through a formalised Health Technology Assessment programme. For now, one or two experts can be available for all the guidelines to help clinicians understand the review process and provide help as and when needed. This may start with an induction/ training webinar to GDG members before the GDG starts and which could be used by all newly inducted members).

#### Box 2.2 Key roles of the clinical members of the GDG

- Contribute towards the development of the guideline scope and drafting of review/clinical questions
- Review existing guidelines which are developed according to international criteria and are relevant to the topic as well as to the country.
- Decide whether recommendations from any of the existing guidelines can be adopted suggest new wording in case adaption is required
- Consider implementation issues arising from recommendations.
- Decide whether all the key clinical issues in the scope are addressed in the selected guidelines for adaptation or if new clinical/ review questions are required
- Contribute constructively to meetings and have good communication and team-working skills; this should include a commitment to the needs of patients and their families.
- With other members of the guideline clinical sub group, agree to the minutes of the GDG guideline meetings.
- Search the literature for updated knowledge and evidence
- Perform systematic review
- Help draft the full guideline document when relevant

#### 2.2.4. Role of the Coordinators

The coordinators oversee and facilitate the whole development process and organises the GDG meetings in consultation with the chair. They are assigned by NCG/TMC to provide administrative and technical support to the GDG, communicate and coordinate with the other experts in GDG.

At present the coordinators have the following responsibilities:

- Collate the data, write up a draft and circulate to the rest of the GDG
- Collect inputs and discuss with the other experts from the GDG
- Convene either a physical or virtual meeting to discuss the guideline draft and inputs
- Draft the full guideline report (see Chapter 6)
- Coordinate with the NCG representatives and send their draft guidelines
- With the GDG Chair, screen the draft guidelines prior to consultation for Quality Assurance (See Chapter 7)

They prepare the draft scope of the guideline with the GDG chair. They also compile existing guidelines developed according to international criteria for guideline development and relevant to the selected topic before the GDG meetings (physical or virtual) with assistance from other members of the GDG (see Chapters 3 & 4). They take detailed notes of meetings and are responsible for writing the guideline in collaboration with other members of the GDG.

#### 2.2.5. Role of patients or patient representatives

Although patients have not been involved in the development of NCG guidelines they should be included as members of the GDG in the future because of their direct experience with the condition. This ensures that issues relevant to patients are included in the guideline development process and inform outcomes of direct interest to them<sup>8,9</sup>. If it is not possible to recruit patients support group members from patients advocacy groups can be co-opted as optional members). However they should not represent the views of any particular organization. Healthcare professionals are well represented in the GDG, so patients usually do not have a healthcare professional background. Patients should have equal status with other members of the GDG. Patients or their representatives may need initial coaching or support from the NCG coordinators to ensure they understand the NCG guideline development and their roles.

### 2.3. Declaring and managing interest

Conflicts of interest (COI) might influence the final recommendations and evaluation of evidence by group members. Therefore potential COI should be recorded at the beginning of the guideline development and at different stages during development. Conflicts of interests can be financial and non-financial<sup>10</sup>. Examples include:

- **A financial conflict of interest** arises when a GDG member receives income or support that is related to, or could be affected by, the outcome of the GDG work. This includes both personal interests and interests of immediate family members of the member. Financial interests include:
  - Personal (or to a family member) financial gain (paid work, consulting income or honoraria) or research, proprietary interests and patents

- grants or fellowships from a commercial entity that has an interest in the topic or the outcomes of the guideline group's work;
  - shares or bonds in a related commercial entity;
  - employment or consultancies
- **Intellectual conflicts of interest** such as authorship of original studies and books that might be potentially included for review. Any potential conflicts of interest of patient members (or their organisation) which may have an impact on power dynamics on their involvement in the GDG.

Any (COI) and how these had been managed should be included in the full guideline report or in a separate appendix (if their publication is not appropriate, they should be made available on request). Any COI-related discussions and any consequent decisions to exclude a member from all or part of the development process should also be reported in the clinical guideline document. The COI should be declared at the time of selection and in case if it arises during the period of guideline development.

### 2.4. Making decisions and consensus

GDG members make collective decisions throughout the development of the guideline. This includes agreeing:

- The clinical/review questions in the scope (see Chapter 3)
- To adopt or adapt recommendations from existing guidelines and new review questions if required (Chapter 4)
- The review protocols for new reviews and agree in interpreting the evidence to answer the questions and developing recommendations (Chapter 5 & 6)

#### 2.4.1 Making decisions

The GDG should work to reach final decisions through a process of discussion and informal consensus based on the evidence available (see Chapters 4, 5 and 6). In the unlikely event there is no unanimous agreement then a voting system may be used... In all cases the approach used should be documented.

The role of the GDG chair in reaching consensus is to ensure that:

- everyone on the committee, including patients/patient representatives, can present their views
- assumptions can be debated
- discussions are open and constructive.

The chair needs to allow sufficient time for all members to express their views and should check that all of them agree to endorse any recommendations. If the GDG cannot come to consensus in a particular area, the reasons for this should be documented in the full guideline report.

### **2.4.2 Making decisions through voting**

If the GDG is unable to agree to recommendations through informal consensus it may use voting to reach its final decisions.

In all these circumstance only the GDG members should participate in voting. They should vote on each recommendation individually and a threshold should be used to approve a recommendation. There are no international rules about an acceptable threshold. For example the American College of Physicians (ACP) uses a 75% agreement among its voters to approve recommendations<sup>11</sup>. If this threshold is not met, the recommendation is discussed further, revised, and voted on again, or removed from the paper. The voting process should be unbiased and therefore votes cast during GDG should be blinded and kept anonymous.

There are several voting procedures available such as the Delphi method<sup>12</sup>, the Nominal Group Technique<sup>13</sup>, consensus Development Conferences. Whichever method is used, rules should be agreed beforehand and clearly documented in the full guideline document. The voting results should be recorded in the minutes of the meeting.

Regardless of the decision-making approach, the transparency of the decision-making process is essential. There should be a clear record of the proceedings and methods used to resolve areas of disagreement. The proceedings from discussions should be recorded and a clear statement provided about the factors considered and the methods used to achieve consensus. A structured summary of the generic and specific issues considered and the key deliberations should be included in the full guideline document (See Chapter 6).

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## Chapter 3. Scoping the guideline and developing key questions

### 3.1. Developing the scope

Defining the scope of the guideline is one of the first and most important tasks in planning its development. The purpose of the scope is to:

- Ensure key clinical issues are covered by the guideline
- Set the boundaries of the guideline, defining what it will include and what it will not include
- Provide a clear structure for the work to focus on the key priorities and to ensure that the development of the guideline is achievable, can be planned within the constraints of time and resources, and is of high quality
- Inform the compilation of existing guidelines that are relevant to the guideline for potential adaptation (See Chapter 4)
- Inform stakeholders about the planned work and its process

### 3.2. The scope content

The scope typically includes a number of sections that covers key structural elements of the NCG guideline. For example, why the guideline is needed, its focus, who it is aimed at, key clinical questions and main outcomes. This allows the GDG to determine the focus of the guideline and the work. Annexure 1 shows a table of the components that the scope should contain. The GDG should use this table as a checklist in planning the development of NCG guidelines to ensure that it follows the main requirements of evidence-based guidelines. An example of a scope is available in Annexure 2 for illustrative purposes<sup>1</sup> (*Please note the example is for a guideline update*). Elements of this scope can be used as a template and can be adapted to the need of individual NCG guidelines. This may be particularly useful when a guideline is adapted from existing guidelines (see Chapter 4).

### 3.3. The scoping process

The scope should be developed through a dialogue with the clinicians, and other members involved in the clinical guideline (through the NCG network and TMC) before the work on the guideline is initiated. The draft checklist should be completed initially by the guideline coordinator and in discussion with the GDG chair. It should be based on the comments received on the previous version of the NCG guideline, including requests from patient groups or other stakeholders (for example funders). This may require consulting with the GDG members and carried out in person or remotely.

### 3.4. Drafting clinical/review questions

Clinical/review questions that will be addressed in the guideline have a strong impact on the final recommendations because they drive the search of evidence, including evidence/recommendations from existing guidelines (See Chapter 4) and systematic reviews (See Chapter 5). Therefore setting the clinical questions is a crucial stage of the guideline development process<sup>2</sup>.

Clinical questions are built on the key clinical issues identified in the scope. These are of clinical importance for India and may not have been covered in the relevant guidelines

identified in the quick search (see Chapter 4) and therefore fill a gap in the guideline. Clinical questions may be drafted by the GDG coordinators. They should then be refined and presented to GDG experts members for discussion. The different perspectives among GDG members will help in ensuring that the right clinical/review questions are identified. The questions might need refining once the evidence has been searched; such changes should be documented (see Chapter 5). Clinical/review questions then inform a) the search for and assessment of existing guideline (See Chapter 4) b) the development of protocols for new reviews if required (see Chapter 5).

Evidence about economic aspects of the key clinical issues should also be considered when developing clinical/review questions. This might include, for example, information about quality of life, rates of adverse effects or use of health services (See Chapter 5 for more details).

### 3.5. Formulating clinical/review questions

A good review question is clear and focused. The nature and type of review questions determines the type of evidence reviews and the type of evidence that is most suitable but the process for developing a review question is the same whatever the nature and type of the question. Review questions usually fall into one of three main areas:

- intervention
- diagnosis
- prognosis

Patient experience is relevant to each of these and should inform the development of a question.

#### 3.5.1. Questions about interventions

Usually, most review questions in clinical guidelines relate to interventions. A helpful structured approach for developing questions about interventions is the PICO (population, intervention, comparator and outcome) framework (see box 3.1). This divides each question into four components:

- Population (the population of interest)
- Intervention (what is being done)
- Comparators (other main treatment options)
- Outcome (measures of how effective the interventions have been).

#### Box 3.1. Features of a well-formulated review question on the effectiveness of an intervention using the PICO framework

**Population:** Which population of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?

**Intervention:** Which intervention, treatment or approach should be used?

**Comparators:** Are there alternative(s) to the intervention being considered? If so, what are these (for example, other interventions, standard active comparators, usual care or placebo)?

**Outcome:** What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning; resource use.

For each clinical/review question, the GDG Coordinator should take into account the various confounding factors that may influence the outcomes and effectiveness of an intervention. Since the aim of guideline recommendations is to achieve improvement (net benefit) it is critical to select the most important outcomes to ensure the guideline is useful. GDG members should identify the key outcomes that will be considered in the guideline. To work effectively the guidelines coordinators may draft an initial list of relevant outcomes for an intervention, its potential benefits and harms (including clinical, equity and costs). The draft list can then be discussed with GDG members who may suggest additional or alternative outcomes. From this, the GDG may rate the importance of each outcome in order of priority (critical for a decision, important or unimportant). It is recommended that a maximum of seven 'critical or important outcomes should be selected as too many outcomes makes it complex to compare across outcomes when weighing the overall benefits and harms<sup>3</sup>. This selection process may take into account issues of implementation and the India healthcare setting where the NCG recommendations will be implemented. For example The NCG has developed a classification of recommendations as '**optional**', '**optimal**' or '**essential**' (according to the Resource stratified classification)<sup>1</sup>. Also see Chapter 6 .

Once the clinical/review question has been agreed, key words can be identified as potential search terms for existing guidelines (see Chapter 4) and the systematic review (see Chapter 5). Examples of review questions on the effectiveness of interventions are presented in box 3.2

### Box 3.2 Examples of questions on the effectiveness of interventions

- What is the effectiveness of exenterative surgery for locally advanced or recurrent rectal cancer? <https://www.nice.org.uk/guidance/ng151/evidence/c5-effectiveness-of-exenterative-surgery-for-locally-advanced-or-recurrent-rectal-cancer-pdf-7029391220> (accessed 9 December 2020)
- In patients with cervical cancer, does presence of histological parameter ABC as compared to absence of histological parameter ABC, result in improved survival? <https://sites.google.com/site/evidencebasedmedicineuos/PICO-Format> ((accessed 9 December 2020)

Review questions about drugs will usually only consider drugs with an India marketing authorisation for some indication. Use of a drug outside its licensed indication (off-label use)

- 
- <sup>1</sup> "**Optional**" is defined as one which would reflect the state of the art, and base its recommendations purely on the available evidence with no consideration for cost effectiveness.
  - "**Optimal**" is defined as recommendations based on both evidence as well as cost effectiveness, but may not be widely available because of issues with expertise and infrastructure
  - "**Essential**" is defined as recommendations based on the evidence, practicality (wide availability of expertise and infrastructure) as well as the cost or treatment and the value it offers. If centres do not have the capabilities to implement these, they should refer patients to a higher centre.

may be considered if this use of the drug is common in India. Drugs without an India marketing authorisation for any indication will not usually be considered in a clinical guideline.

### 3.5.2. Questions about diagnosis

Clinical/review questions about diagnosis are concerned with the performance of a diagnostic test (physical examination, history taking, laboratory or pathological examination and imaging tests)

Broadly, questions about a diagnostic test are of three types:

- questions about the diagnostic accuracy of a test or a number of tests individually against a comparator (the reference standard)
- questions about the diagnostic accuracy of a test strategy (such as serial testing) against a comparator (the reference standard)
- questions about the clinical value of using the test.

The PICO framework described in the previous section is useful when formulating review questions about diagnostic test accuracy (see box 3.1). The intervention is the test under investigation (the index test[s]), the comparison is the reference standard, and the outcome is a measure of the presence or absence of the particular disease or disease stage that the index test is intended to identify (for example, sensitivity or specificity). The target condition that the test is intended to identify should be specified in the question. These components are presented in Box 3.3. An example of a question on the accuracy of a diagnostic test are given in box 3.4.

#### Box 3.3. Features of a well-formulated review question on diagnostic test accuracy using the PICO framework

**Population:** To which populations of patients would the test be applicable? How can they be best described? Are there subgroups that need to be considered?

**Intervention** (index test[s]): The test or test strategy being evaluated.

**Comparator:** The test(s) with which the index test(s) is/are being compared, usually the reference standard (the test that is considered to be the best available method to establish the presence or absence of the condition of interest – this may not be the one that is routinely used in practice).

**Target condition:** The disease, disease stage or subtype of disease that the index test(s) and the reference standard are being used to establish.

**Outcome:** The diagnostic accuracy of the test or test strategy for detecting the target condition. This is usually reported as test parameters, such as sensitivity, specificity, predictive values, likelihood ratios, or – where multiple cut-off values are used – a receiver operating characteristic (ROC) curve.

**Box 3.4 Example of review questions on diagnostic test accuracy**

- Which of the following, alone or in combination, constitutes the most clinical and cost- effective pathway for diagnosing prostate cancer:
  - Multiparametric or biparametric MRI alone
  - MRI influenced TRUS biopsy (MRI-targeted and MRI-guided
  - TRUS biopsy)
  - TRUS biopsy alone (systematic)
  - Transperineal template biopsy

From: <https://www.nice.org.uk/guidance/ng131/evidence/d-diagnosing-and-identifying-clinically-significant-prostate-cancer-pdf-6779081777> (accessed 9 Dec 2020)

Although the assessment of test accuracy is important in establishing the usefulness of a diagnostic test, the clinical value of a test is its usefulness to guide treatment decisions, and to improve patient outcomes. Questions aimed at establishing the clinical value of a diagnostic test in practice can be structured in the same way as questions about interventions. Questions about the safety of a diagnostic test should also be structured in the same way as questions about interventions.

**3.5.3. Questions about prognosis**

Prognosis describes the likelihood of a particular outcome, such as the progression of a disease, or the survival time for a patient after the diagnosis of a disease or with a particular set of risk markers. Prognostic information can be used in guidelines to:

- provide information to patients about their prognosis
- classify patients into risk categories (for example, cardiovascular risk) so that different interventions can be applied
- define subgroups of populations that may respond differently to interventions
- identify factors that can be used to adjust for case mix (for example, in explorations of heterogeneity)
- help determine long-term outcomes not captured within the timeframe of a clinical trial (for example, for use in an economic model).

Review questions about prognosis address the likelihood of an outcome for patients from a population at risk for that outcome, based on the presence of a proposed prognostic factor. These may be closely related to questions about interventions if one of the prognostic factors is treatment and can be structured in the same way as questions about interventions. Examples of review questions relating to prognosis are given in Box 3.5.

### Box 3.5 Examples of review questions on prognosis

- What is the risk of lung cancer in patients presenting in primary care with symptom(s)?  
From: <https://www.nice.org.uk/guidance/ng12/evidence/appendix-g-pdf-74333344> (accessed 09 Dec 2020)
- What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?  
From: <https://www.nice.org.uk/guidance/ng99/evidence/a-investigation-management-and-followup-of-glioma-pdf-4903134734> (accessed 23 February 2021)

### 3.5.4 Questions that consider cost-effectiveness

It is useful to define priorities for economic evaluation whilst defining the scope of the guideline, and when clinical/review questions are developed. Questions on economic issues mirror the questions on effectiveness but these have a focus on cost effectiveness. This might include, for example, information about quality of life, rates of adverse effects, preventing disease, or use of health services. An example of a review question relating to cost-effectiveness is given in Box 3.6.

### Box 3.6. Example of a PICO Question on Cost-effectiveness

Is breast cancer screening in women 70 years of age or older with an average risk of breast cancer as cost-effective as no screening in preventing death from breast cancer ? from:  
[https://apps.who.int/iris/bitstream/handle/10665/145714/9789241548960\\_eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/145714/9789241548960_eng.pdf?sequence=1&isAllowed=y) (accessed 18 February 2021)

Methods for identifying and reviewing the economic literature and economic analyses are covered in chapter 5.

When the scoping checklist, the clinical/review questions and key outcomes have been developed this should enable a more detailed search for existing guidelines that are relevant to the clinical guideline being developed (see Chapter 4) and to identify new reviews if needed (See Chapter 5)

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3. World Health Organization. (2014). WHO handbook for guideline development, 2nd ed. World Health Organization. <https://apps.who.int/iris/handle/10665/145714>

## Chapter 4. Using and adapting existing guidelines

### 4.1. Introduction

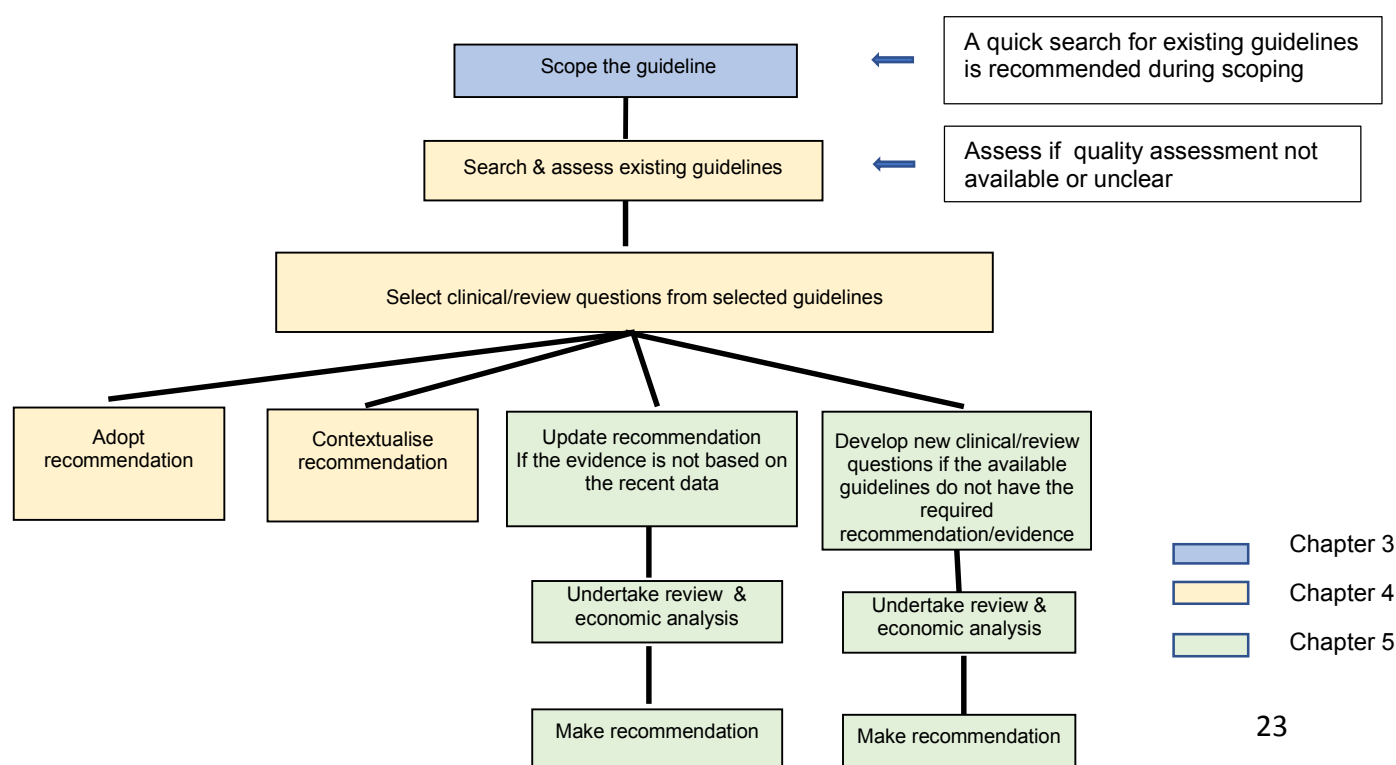
Developing de novo clinical guidelines is expensive, time consuming and requires dedicated teams of methodologists and experts. These financial and human resources are not available in most guidelines programmes, making the opportunity costs of de novo guideline development questionable. As an alternative, countries are increasingly using existing guidelines that can be adapted to fit their local needs. Adaptation has been defined as:

*“The systematic approach to considering the use and/or modification of a guideline developed in one cultural or organizational setting for application in a different context. Adaptation can be considered as an alternative to de novo guideline development<sup>1</sup>”*

This approach seems well suited to developing the NCG guidelines. However there is currently no internationally validated methodology for how to adapt clinical guidelines. Different approaches have been reported, including adopting, adapting or contextualising existing high-quality guidelines to make recommendations relevant to local contexts<sup>2,3,4,5,6</sup>. The proposed approach in the NCG guideline manual draws from these experiences. It aims to include a mix of pragmatism and rigour through a transparent and inclusive process, which is contextualised to the needs of India and, importantly is feasible for the NCG guidelines programme at this stage. It follows broad accepted principles that the adaptation process: *“ensures that the final recommendations address specific health questions relevant to the context of use, and address the needs, priorities, legislation, policies and resources in the target setting without undermining the validity of the target recommendations<sup>1</sup>”*

The process of using and adapting guidelines entails several steps that define/inform the development path of the guideline and therefore it is mentioned in different chapters of this manual. The adaptation process and associated chapters are illustrated in Graphic 4.1

**Graphic 4.1. Process of using and adapting NCG guidelines and linkages between the NCG manual chapters**





## 4.2. Searching relevant guidelines

The first step in using existing guidelines is to search for guidelines that are relevant to the NCG guideline (similar end users and patients). This is best undertaken during the scoping stage and once the patient/clinical pathway has been drafted (see Chapter 3). A simple search undertaken by the NCG coordinators may be sufficient to highlight a wealth of good quality cancer guidelines that cover substantial elements of the NCG guideline clinical pathway. For example there are international guideline programmes that contain trustworthy and evidence-based cancer guidelines and that are usually freely available on the internet. These include:

- National Institute for Health and Clinical Excellence (NICE) UK <https://www.nice.org.uk/guidance/conditions-and-diseases/cancer>
- National Health and Medical Research Council (NHMRC) Australia <https://www.clinicalguidelines.gov.au>
- Scottish Intercollegiate Guidelines Network (SIGN) Scotland <https://www.sign.ac.uk>

A reliable guideline database is the Emergency Care Research (ECRI) database. <https://guidelines.ecri.org/#>, that operates on behalf of the National Guidelines Clearinghouse in the United States. The database provides some guideline-related content; including *Guideline Snapshots* (a tool to screen and quickly identify a guideline's focus, patient population, and major interventions); *Guideline Briefs*: Succinct summaries of key elements of a clinical guideline. *TRUST* (Transparency and Rigor Using Standards of Trustworthiness) *Scorecards*: Appraisals which rate the extent to which a guideline adheres to the National Academy of Medicine (formerly the Institute of Medicine [IOM]) Standards for Trustworthy Guidelines. To maximize time and resources available, guidelines selected through the ECRI do not need to be reassessed.

In addition, on the basis of their knowledge and expertise GDG members may know of cancer guidelines that are commonly used in clinical practice or search web sites of relevant medical societies/organisations to identify such guidelines. These include:

- The American Society of Clinical Oncology (ASCO) <https://www.asco.org/research-guidelines/quality-guidelines/guidelines>
- European Societies: European Society for Oncology (ESMO) <https://www.esmo.org/guidelines>; European Society of Gynaecological Oncology (ESGO) <https://www.esgo.org/explore/guidelines/>

Other international clinical guidelines portals contain link to guidelines on oncology, such as the Guidelines International Network (G-I-N) library of guidelines: <https://guidelines.ebmportal.com>. However, the quality of some guidelines is unknown. If guidelines are selected from such sources they should be assessed before use if a quality report is not available (see Section 4.3)

The search should include guidelines published in English no earlier than 5 years before the work on the NCG guideline starts or were updated during this time span.

### 4.3. Assessing source guidelines

Once potential relevant 'source' guidelines have been identified, the second step is to screen their methodological quality to ensure they are based on credible evidence and meet international development criteria (*unless they already have a quality assessment*). One of the most reliable tools is the AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument (<http://www.agreetrust.org/>) that is widely used to evaluate the scientific quality of a whole guideline, based on documentation of its development process.

To be considered as a source guideline it should have a full document that contains, as a *minimum* : the clinical /review (PICO) questions, details of search strategies, evidence reviews and their summaries, including GRADE tables and links between evidence and recommendations, according to international standards. This assessment is likely to be carried out by the NCG guidelines coordinators and in discussion with the GDG chair. The number of selected guidelines after assessment may need to be reduced if there are more than can realistically be dealt with by the GDG. This assessment is likely to be carried out by the NCG guidelines coordinators and in discussion with the GDG chair.

There is no cut-off point for accepting or rejecting a source guideline. However, the results of the assessment should be documented in the methods section of the full guideline document, (see Chapter 6).

#### 4.3.1. Selecting/prioritising clinical/review questions

The main *clinical review questions* would have been drafted up front during the scoping of the NCG guidelines (see Chapter 3). These can be refined or modified using recommendations from the selected source guidelines so they are relevant to India. If time allows, one possible approach is to list about 10-15 clinical questions (PICO) questions and send these to GDG members through an online survey asking them rate the relative importance /relevance of these questions for the India setting, asking them to consider factors such as matching of population, availability of interventions and potential barriers for implementing them. This process will be done by the coordinators.

When a source guideline does not cover an area judged to be a priority in the NCG guideline \_and that is covered in its scope\_ the GDG may decide to develop a new clinical/review. In this case this will require a new review of evidence in line with the 'de novo guideline development process' (see Chapter 5).

#### 4.3.2. Assessing recommendations from source guidelines

The next step in the adaptation process entails assessing the *recommendations* from the selected clinical/review questions of the source guidelines. There are two parts to this:

The first part is to ensure each recommendation links with the evidence in line with international criteria, such as the GRADE (Grading of Recommendations, Assessment, Development and Evaluations)<sup>7</sup> and how the final decisions were reached. GRADE is now considered best practice by many international guideline developing institutions, including WHO and NICE.

#### 4.3.2.1. Appraising the quality of evidence

The GRADE approach assesses the quality (or certainty) of a body of evidence. After deciding the clinical question, population and the most important outcomes guideline developers rate the quality of evidence, which is best applied to each outcome. GRADE distinguishes two definitions of quality: 1) the quality of evidence that reflects the confidence that the estimates of the effect are correct; 2) In the context of making recommendations, the quality reflects the confidence that the estimates of an effect are adequate to support a particular decision or recommendation<sup>8</sup>. In making these judgements GRADE considers the following factors underpinning the body of evidence:

- risk of bias
- precision of the effect estimates
- consistency of the individual study results
- how directly the evidence answers the question of interest
- risk of publication or reporting biases

GRADE specifies four categories for the quality of evidence:

**High:** The guideline developers have a lot of confidence that the true effect is similar to the estimated effect

**Moderate:** The guideline developers believe that the true effect is probably close to the estimated effect

**Low:** The true effect might be markedly different from the estimated effect

**Very low:** The true effect is probably markedly different from the estimated effect

[GRADE](#) tables describe the number, type and quality of the studies for each [review question](#) and provide an overall rating of confidence (high, moderate, low or very low) in estimates of effect for each outcome. GRADE tables are likely to be compiled by the coordinators and presented to the GDG. Templates and relevant documents can be accessed on the GRADE website: <https://www.gradeworkinggroup.org> and <https://gradepro.org>

An example of a completed GRADE table on Optimal duration of adjuvant chemotherapy for colorectal cancer is available at: <https://www.nice.org.uk/guidance/ng151/evidence/c8-optimal-duration-of-adjuvant-chemotherapy-for-colorectal-cancer-pdf-253058083669> (appendix F)

Using the GRADE tables, the GDG should agree that the reviews are a fair summary of the evidence and should discuss any uncertainty, including the presence, likely magnitude and direction of potential biases.

#### 4.3.2.2. Acceptability and applicability of source recommendations

The second part of the assessment relates to the acceptability and applicability of the source recommendations and use of recommendations in practice. This depends on the differences

in the cultural and organisational context, including the availability and organisation of health services, expertise, and resources, as well as population characteristics, beliefs and value judgements. These variables are particularly important when adapting guidelines for culturally sensitive interventions and technological innovations. The ADAPTE Resource Tool Kit<sup>9</sup> provides a useful framework in asking the following (adapted) questions for each recommendation:

- Does the population described for eligibility match the population of patients to which the recommendation is targeted in India, are subgroups of importance covered in the recommendations (acceptable)?
- Are the interventions and/or necessary equipment available in the healthcare setting under consideration (hospitals in India)? (applicable)
- Is the necessary expertise (knowledge, skills, training) available in the health care setting (hospitals in India) or does the recommendation require additional investments? (applicable)
- Are there any constraints, organisational barriers, policies, and/or resources in the health care setting (hospitals in India)? (applicable)
- Is the recommendation compatible with the culture and values in the health care setting (hospitals in India)? (acceptable and applicable)
- Do the benefits (health and costs) to be gained from implementing this recommendation make it worth implementing (acceptable)

Annexure 3 contains an evaluation sheet adapted from the ADAPTE Tool Kit to help evaluate the acceptability and applicability of recommendations from the source guideline(s). This might be undertaken by the coordinators, and the results presented to GDG members.

### 4.4. Making recommendations

Transferring recommendations from source guidelines can be challenging because NCG guidelines are designed to be used in the Indian setting, which is likely to be very different from the setting of the source guideline. When making recommendations from a source guideline the GDG should consider the followings:

Based on the selected recommendations, the GDG will make its final judgements through discussions that take into account prioritization considerations specific to India. These include recommendations that:

- Are likely to have a high impact on key outcomes
- Are likely to have a high impact on reducing variation in care and outcome in India
- Relate to an intervention that is not part of routine cancer care in India
- Require major changes in service delivery
- Are expected to be implemented under the Health Benefits Package of the AB-PMJAY Scheme (see Chapter 6)
- Are cost effective (see Chapter 5)

**Note:** The above criteria are similar to those considered in developing the scope. They help prioritise the development/adaptation work

The coordinators may draft proposals ahead of the GDG meeting to use time efficiently. However sufficient time should be set aside for the GDG to discuss the proposed options. These options are outlined below:

### **1) *Adopt a recommendation\****

This entails reproducing a recommendation verbatim from the source guideline. Recommendations are adopted when they can be applied directly, without any changes, to the Indian context (see note below).

### **2) *Contextualise a recommendation to India\****

This means, reproducing a recommendation verbatim from the source guideline but adding a commentary about local context conditions needed for implementing the recommendation. Contextual points can include comments relating locally-appropriate alternative methods of intervention delivery, system issues that would need to be considered to be implemented in the current India care system.<sup>12</sup>

**Note:** this may also include: minor edits to clarify the recommendation. An. Example of such edit is presented in Box 4.1. However, the edits should be consistent with the evidence on which the source recommendation was based. If not, the GDG should explain the changes and the new wording, or develop a new review question (see Chapter 5).

#### **Box 4.1. Example of an edited recommendation from a Cancer Care Ontario (CCO) Guideline<sup>1&10</sup> by the American Society of Clinical Oncology (ASCO)<sup>2&11</sup>**

<sup>1</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4381792/>

<sup>2</sup> <https://ascopubs.org/doi/10.1200/JCO.2016.67.0182>

<b>Original CCO Guideline clinical Topic:</b> Concurrent administration of adjuvant trastuzumab and non-anthracycline chemotherapy regimens (CCO Recommendation 31)	
<b>Recommendation in CCO guideline (source guideline)</b>	<b>Adapted ASCO recommendation</b>
Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen.	Trastuzumab should be preferentially administered concurrently (not sequentially) with a non-anthracycline chemotherapy regimen
<b>Rationale for editing wording:</b> The ASCO Panel adapted the CCO recommendation to indicate a preference for concurrent versus sequential administration of trastuzumab and non-anthracycline chemotherapy	

### **3) *Update a recommendation***

This arises when the evidence underpinning a recommendation needs updating in the light of recent research. For example GDG members may be aware of relevant studies that may have implications for making the recommendations. These studies or new research may not change the recommendation but they need to be reviewed according to international standards (see Chapter 5).

\* some recommendations from source guidelines are based on cost-effectiveness analysis and other considerations that are specific to the health system for which they were developed, that may not be applicable to India. In such cases it is advisable to use the clinical evidence from the source recommendation and undertake a separate health economic analysis for India before making a final recommendation (See Chapter 5)

### **4.5. Resource stratified guidelines**

When using and adapting existing guidelines the GDG should consider the following factors in making the final recommendations/decisions that may influence their implementation: weighing up the consequences and impact of the recommendations in practice, acceptance by clinicians and/or patients, cultural relevance, local contexts, availability of care, affordability, equity and access.<sup>13</sup> They may also take into consideration the likely cost-effectiveness of alternative interventions in the context of the India healthcare system (see Chapter 5). These considerations may guide the NCG classification of Resource stratified recommendations mentioned in Chapter 3: “Optional”, “optimal” or “essential” (See Chapter 6)

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## Chapter 5. Incorporating economic evidence in NCG Guidelines

### 5.1 Introduction

Every country has a finite amount of resources for health and many, including India, are making strides towards achieving universal health coverage. To ensure the maximum number of patients are getting access to the care that they need, it is necessary to make explicit choices about what to buy within the available budget<sup>1</sup>. It is important to be transparent about these choices and ensure that they are based on the best available evidence on both the impact and costs of the health service. Economic evidence includes information on costs, benefits, resource use and cost-effectiveness which together help inform the budgetary implications, value for money (efficiency) and fairness of any treatment choices<sup>2</sup>.

The purpose of this chapter is to generally discuss how economic evidence can be used to inform clinical guidelines across India's National Cancer Grid (NCG), irrespective of the payer<sup>3</sup>. It clarifies why economic evidence is important, how the Guidelines Development Group (GDG) might choose different approaches to generating economic evidence based on the research questions defined in Chapter 3 and the existing availability of evidence. These different approaches - the most common of which is cost-effectiveness analysis - are then described. The chapter concludes with a brief description of how this evidence might be used in decision making.

### 5.2 The importance of economic evidence for NCG guidelines

The burden of cancer and cost of cancer treatment are both disproportionately high in India compared with the health system as a whole.

In considering cancer guidelines which may be implemented in the NCG centres, incorporating economic evidence into decision making has several important benefits. First, it can ensure that the maximum gain is achieved for patient health, focusing health services on high-priority interventions. Second, it may present opportunities to achieve economies of scale and standardise pricing in procurement of medicines and commodities, which can increase the overall number of patients reached. Finally, it can reduce heterogeneity in cancer care ensuring more consistent and equitable treatment between patients.

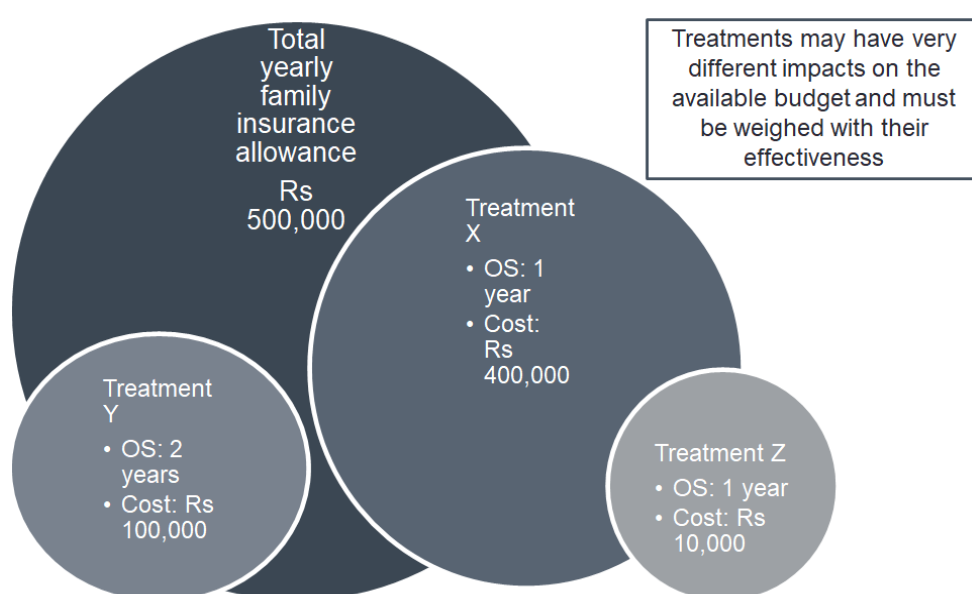
Additionally, incorporating economic evidence helps to identify where public and individual resources can be freed up for other uses, yielding benefits to individuals, families, and the entire health system. Without using such evidence to inform funding decisions within and beyond cancer care, there can be potential downstream adverse consequences for the overall finance budget. For example, in Colombia in 2011, just 58% of children had been fully vaccinated, an intervention that was considered to be highly cost-effective, i.e. is very low cost relative to the number of lives potentially saved. At the same time, branded bevacizumab (Avastin) had been approved for treatment of breast cancer in Colombia under publicly funded health insurance even though it had been deemed not cost-effective and indeed not safe even in the United States<sup>4</sup>. The use of

economic evidence could have provided insight into the most cost-effective treatments to include under the public health insurance scheme to provide the greatest health impact.

Decisions to recommend an intervention within standard treatment guidelines may also inform the treatments that are made routinely accessible in India under the national health insurance programme, and should therefore be sensitive to potential budget constraints. In the context of India's PM-JAY insurance scheme there is a limit of ₹5 lakhs per family per year via cashless health benefits for all secondary and tertiary care including cancer<sup>5</sup>, or for an individual covering their own treatment costs. Oncology care is generally expensive, and therefore difficult decisions on trade-offs between treatment options need to be made to ensure that the care remains within budget (Figure 1).

Using economic evidence to develop the guidelines can help inform those decisions, avoid similar scenarios and ensure that all patients receive care that takes into account financial sustainability with minimal or no compromise in acceptable standard of care.

**Figure 1: Treatments in relation to budgets**



**Case Study. Trastuzumab for the adjuvant treatment of patients with nonmetastatic breast cancer in India.**

Breast cancer has a significant disease burden in India, comprising 27% of all cancers in the country, therefore there is a need for effective treatments.<sup>37</sup> Trastuzumab has been found to demonstrate considerable improvements in disease-free survival and overall survival, but is not widely used due to its expense<sup>38–41</sup>.

A recent cost-effectiveness analysis in India found that treatment with trastuzumab for shorter regimens (9 weeks and 6 months were modelled) would be considered cost-effective, meaning that the incremental costs and associated survival benefits associated with trastuzumab would be justifiable<sup>39</sup>. However, the costs of a longer one-year regimen would potentially exceed the possible benefit, and there would be more value to the health system if these funds were spent elsewhere. Should the National Pharmaceutical Pricing Authority negotiate a price reduction by 35%, then prescribing trastuzumab for the longer one-year would then be considered cost-effective.

Without the analysis, it would be difficult to justify prescribing trastuzumab. However, the economic evidence provides a transparent and informed insight into how the benefits are determined in relation to the costs. Given the evidence on the shorter regimens which suggests they are cost-effective, it is reasonable for them to be incorporated into the guideline<sup>39</sup>.

### **5.3 Economic evaluation evidence**

It is vital for a clinical guideline to recommend safe, effective treatments that provide the maximum possible gain in outcomes within the resources available. However, it can be challenging to determine this without conducting an additional analysis. Generating economic evidence is usually done through an economic evaluation which forms part of a process called Health Technology Appraisal (HTA)<sup>6</sup>. The results of the economic evaluation and broader HTA can be used to provide an evidence-based recommendation on the most appropriate treatments to include in a guideline.

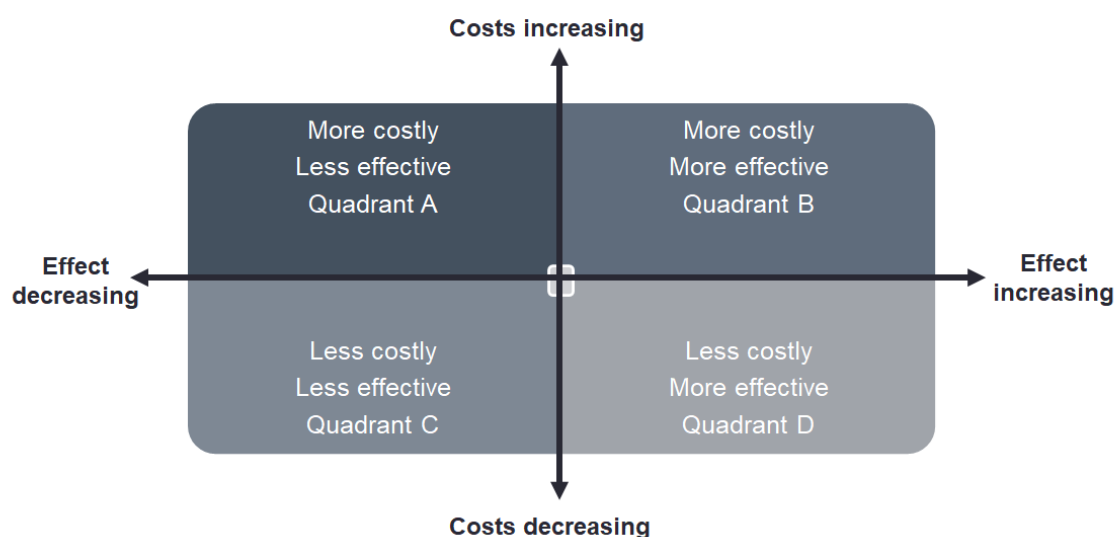
Economic evaluation is a mechanism for comparative analysis between treatments to determine their value for money. A common misconception is that economic evaluation is only concerned with costs. In fact, an economic evaluation quantifies the difference in overall survival, disease progression and the quality of life between treatments which it turns into a single unit of benefit (e.g. cost per life year gained, deaths averted). It then calculates the associated cost of this benefit.

Treatments may extend overall survival, or they may slow progression delaying the need for surgery or changing treatments. An economic evaluation can capture the benefit of both. It can also capture the difference in outcomes from the safety profile of a treatment, which is particularly relevant if a treatment is associated with more serious adverse events.

The costs associated with a treatment are multi-faceted and reflect the costs of treatment, monitoring, adverse events, and associated resource use which all feed into the analysis to capture the total costs and cost savings to the health system. For example, two treatments may have the same list price, but if one is administered in a hospital setting by subcutaneous injection then it is likely to generate larger costs to the health system than tablets that can be self-administered at home. If the two treatments have the same effectiveness, it could potentially be more cost-effective for the tablets to be included in the guideline.

By weighing the associated costs and benefits of a treatment, economic evaluation can provide insight into its value. There is a strong justification for treatment to be incorporated into a guideline if it is cost saving and with either equal or improved outcomes. Conversely, if a treatment is costlier and has equal or worse outcomes than its comparator, then the guideline should recommend alternative options (Figure 2: A & D).

**Figure 2: Cost-effectiveness plane**



For treatments in quadrants B and C of Figure 2, the results of the economic evaluation can be used to assess the financial sustainability of their incorporation into the guidelines. If a treatment improves outcomes at a higher cost, then the results of the evaluation can be used to consider the affordability of the treatment. If a treatment is less effective but also less costly, then the results of the economic evaluation can be used to consider whether the difference in costs frees up sufficient resources to justify the difference in outcomes<sup>7</sup>.

Incorporating evidence from economic evaluations into clinical guidelines can help improve the efficiency of the health system by identifying and prioritising effective affordable treatments that provide the most value for money. This will be vital for the sustainability of the health benefits package under the PM-JAY and will allow families to maximise their allocated funds and achieve their optimal health benefits.

## 5.4 Generating economic evidence

If the GDG wants to incorporate economic evaluation evidence, then the first step is to clearly define the research question and outline a protocol (see Annex 4).

The GDG should then conduct an initial targeted search of the literature to gain an insight into the published evidence. The goal of the search will be to:

1. Confirm whether the question has already been answered in the Indian context;
  - a. All results should be validated through discussions with key government bodies, clinicians and health economists;
2. Search for whether a review has been done in a subset of pre-selected countries with established HTA agencies;
3. Collate relevant abstracts to gain an understanding of the safety, efficacy, and cost-effectiveness of the intervention from a broad range of perspectives (a methodology used in Canada could be replicated<sup>8</sup>).

The main purpose of the review should be to determine whether the technology or intervention under consideration represents good 'value for money' in India. In other words, it should determine whether the additional cost of the technology is justified by the outcomes it achieves compared with the standard of care.

The results of the review may identify robust and reliable analyses which can be used directly. There would be no reason to proceed with the research question if:

- The intervention has no likelihood of being cost saving and its harms outweigh its benefits;
- There is no clinical evidence of a benefit;

Further action may also not be necessary if:

- There is very strong evidence for the benefits which clearly outweigh the costs;
- An intervention has very small costs, very small benefits and very small budget impact.

However, it may still be necessary to substantiate this with additional evidence (see below).

For most research questions the results of the review may not be so straightforward, there might be gaps in the available evidence, or the evidence available might not be translatable to India (Chapter 4). In these instances it may be necessary to conduct a new analysis or economic evaluation to generate and appraise the appropriate evidence as to whether the intervention should be included in the guideline.

There are multiple approaches to generating economic evidence, as detailed in Table 1. Cost-effectiveness analysis and budget impact analysis are the most common and comprehensive approaches, but conducting a new analysis demands additional expertise, time and data. Depending on the evidence constraints there are also alternative options for generating evidence

on the cost-effectiveness of an intervention. The outputs of all approaches can facilitate estimates of the cost-effectiveness of a treatment. However, in using these differing approaches it is always important to consider whether the results are applicable to India. For further information on these approaches, please review the relevant section.

Table 1: Strengths and limitations of different approaches to generating economic evidence

Approach	Output	Strengths	Limitations	For more details, see section
Cost-effectiveness analysis and budget impact analysis	India specific estimates of cost-effectiveness	<ul style="list-style-type: none"> <li>- Robust</li> <li>- Comprehensive</li> <li>- Specific to India</li> <li>- Provides comparison between treatments</li> <li>- Determines the cost of the incremental benefit</li> <li>- Facilitates the assessment of the impact to the health system</li> <li>- Can test the uncertainty of the results</li> </ul>	<ul style="list-style-type: none"> <li>- Time-consuming</li> <li>- Data-intensive</li> <li>- Requires expertise in health economics</li> <li>- India specific data might not be available</li> <li>- There may be considerations outside of cost and clinical benefit that will not be reflected in the analysis</li> <li>- Difficult to establish which treatments are considered to be cost-effective in India due to the lack of threshold</li> </ul>	5.5 5.6
Cost-effectiveness model adaptation	Estimates of cost-effectiveness adapted for India	<ul style="list-style-type: none"> <li>- Makes use of an existing model</li> <li>- Can incorporate local data</li> </ul>	<ul style="list-style-type: none"> <li>-Time-consuming</li> <li>-Data-intensive</li> <li>-Requires expertise in health economics</li> <li>-Depends on the underlying model being structurally relevant to the research question</li> <li>-May not be different in capacity and time requirements compared with a de novo CEA</li> </ul>	5.7.1
Literature review	Estimates of cost-effectiveness from the	<ul style="list-style-type: none"> <li>- Transparent methods</li> <li>- May be comprehensive (systematic reviews)</li> </ul>	<ul style="list-style-type: none"> <li>- May be time consuming</li> <li>- Evidence may not be transferable to the Indian setting</li> </ul>	5.7.2

	published literature	- Summarizes relevant empirical literature	- Requires expertise in evidence synthesis - May only account for safety and efficacy	
Price benchmarking	The price paid by India in relation to other countries	- Quick way to identify drugs that are likely not cost-effective in India - Minimal additional capacity necessary - Can be used for price negotiations	- Confidential discounts may skew benchmarking results - Only for drugs and not other technologies - Data might not be generalisable to India - Price variation of branded vs generics + biosimilars	5.7.3

If it is necessary to generate economic evidence, then it is important to choose the method that reflects the skill set, data constraints and time available.

In addition to considering the strengths and limitations of these methods, it is important to consider the possible limitations of using economic evidence once generated. Due to the fragmented eco system, it may be challenging to institutionalise the findings across the health system as different institutions are responsible for putting the recommendation into practice. The results also might not fit into the established recommendation categories of optional, optimal and essential. It can be difficult to determine what is considered good value for money in India, and what would be too expensive. Finally, there may be considerations outside of costs and clinical benefits that should feed into decision making.

Despite these limitations, the use of economic evidence can still provide valuable insight into the value of treatments, and will assist in informing the guideline and making the decision process surrounding recommendations more transparent, evidence based and robust.

### 5.5 Economic evaluation methods: cost-effectiveness analysis

There are multiple approaches to conducting an economic evaluation. One approach commonly used in India to assess the value of cancer treatments is a cost-effectiveness analysis (CEA), which is the focus of this section. Other forms of analysis will not be considered in this chapter but details are available elsewhere<sup>2</sup>. CEAs are analytical models that can be used to inform whether the adoption of a technology is considered to be a cost-effective use of resources. This chapter will focus on the cost-effectiveness of drug treatments, however there are multiple technologies that can be assessed with a CEA (e.g. surgery, diagnostics, devices, vaccines etc).

Importantly, to ensure consistency in economic evaluations, a reference case has been developed by the Department of Health Research, under Health Technology Assessment in India

(HTAIn). The HTAIn Reference Case<sup>9</sup> provides guidance on how methods and data collection of any CEA analysis should be conducted and reported in India. There are also other organisations that have produced useful guidelines<sup>10</sup>. Adhering to the reference case increases quality, transparency and consistency which ultimately facilitates the interpretation of the results. In this section, we provide a general overview of CEA, but the Reference Case presents a more comprehensive guide to economic evaluation conduct in the Indian context.

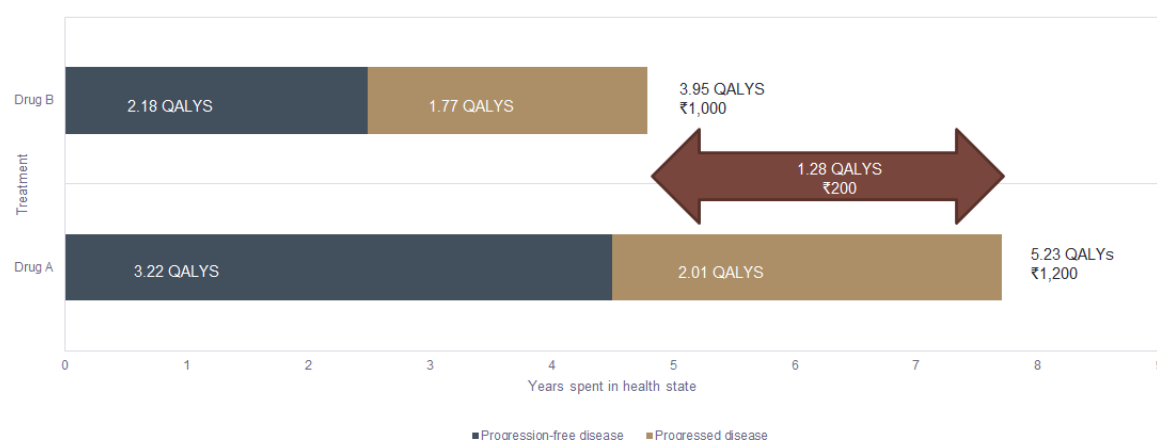
CEA evaluates whether a new intervention provides an efficient use of resources compared with the standard of care by modelling natural history, treatment pathways, associated resource use and costs, and predicted health outcomes.

A CEA model is constructed to reflect the main stages of disease progression, for example progression-free disease, progressed disease and death. For each stage, the model estimates the predicted resource use and associated costs e.g. consultations with an oncologist, scans and laboratory tests. The model then compares how quickly patients progress with the different treatments (“comparators”) based on evidence from either clinical trials, systematic reviews or other analyses.

Using this framework, the CEA estimates the differences between comparators in the costs generated to the health system. Whilst drug costs are often a significant driver of cost-effectiveness, a treatment may sufficiently displace other costs which would render its adoption to be cost-effective. For example, a treatment may have a high drug cost, but this could be offset if the treatment significantly delays disease progression and subsequent surgery costs.

CEA presents the clinical benefit of a treatment by using a measurement called a “quality-adjusted life year” (QALY)<sup>11</sup>. One year of life lived in full health is equal to one QALY. The QALYs generated by the treatment reflect both the overall survival and the years spent progression-free and with disease progression. This is calculated by multiplying the years spent in each disease stage with a quality-of-life score known as a ‘utility value’<sup>12</sup> which is on a 0 to 1 scale. Using a summary outcome measure such as a QALY creates a consistent unit of health measurement which facilitates the understanding of cost in relation to the generated benefits. CEA results are illustrated in Figure 3.



**Figure 3: Illustrative CEA results**

CEA ultimately determines the incremental costs to the health system and the associated benefit of a new intervention in relation to its comparator. The results are presented as a single ratio to determine the incremental cost per QALY, otherwise known as the “incremental cost-effectiveness ratio” (ICER)<sup>13</sup>.

#### Equation 1: ICER Equation<sup>14</sup>

$$\begin{aligned}
 \text{Incremental costs} &= \text{Total costs (intervention)} - \text{Total costs (comparator)} \\
 \text{Incremental QALYs} &= \text{Total QALYs (intervention)} - \text{Total QALYs (comparator)} \\
 \text{ICER} &= \text{Incremental costs} \div \text{Incremental QALYs}
 \end{aligned}$$

If a treatment is cost saving and improves outcomes (quadrant D Figure 2), the ICER is considered to be ‘dominant’. If a treatment increases costs to the health system and worsens outcomes (quadrant A Figure 2), the ICER is considered to be ‘dominated’. The decision to include treatments from quadrant D and A in the clinical guidelines is considered to be relatively straightforward, yes, and no, respectively.

However, for other treatments (quadrants B + C Figure 2), the ICER can be considered whilst assessing the financial sustainability of their adoption.

The ICER reflects the cost to the health system with the adoption of the new technology for one unit of health benefit (1 QALY). If the ICER is low, then the cost of the benefit to the health system on a per patient level is considered to be modest. As the ICER increases, so do the associated costs to the health system for one QALY. A high ICER may suggest that the cost to the health system is excessive in comparison to the benefits that the treatment generates.

In order to inform future guideline development, it may be beneficial to create a database that records the ICERs of treatments that have been assessed by the NCG for inclusion in the clinical guidelines.

It is important to remember that the results of the ICER are on a per patient level. To understand the cost to the health system of treating all patients, a budget impact analysis should be conducted.

## **5.6 Budget impact analysis**

Whilst an intervention may be cost-effective, it is still necessary to determine whether it is affordable.<sup>15</sup> This is vital for the development of a clinical guideline as the introduction of a treatment into the clinical pathway should not adversely affect the long-term financial stability of the health service<sup>16</sup>. This is particularly relevant in the construction of a health benefits package.

Budget impact analysis (BIA) estimates the financial consequences of adoption and diffusion of a new health care intervention within a health care setting. Specifically, BIA predicts how a change in the use of a technology will impact the trajectory of spending on a particular health condition<sup>17</sup>.

The benefit of BIA is that costs are applied to the number of predicted patients which provides a clearer estimate of the financial impact of including a treatment in the clinical pathway. This is particularly important for treatments that are expected to receive a high volume of uptake or are highly costly.

BIA is conducted over a fixed time period, often one to five years, and can capture the financial benefit of interventions that are costly to implement but save money over the long term.

## **5.7 Other approaches to generating economic evidence**

Other less-intensive approaches to generating economic evidence are also possible and may be well-suited to some research questions when carrying out the 'gold standard' of CEA is not possible, or to precede a CEA to determine whether more detailed analysis is necessary<sup>18,19</sup>. In this section, we summarize three general approaches: adapted CEA, literature review, and price analysis.

### **5.7.1 Cost-effectiveness model adaptation**

Conducting CEA from scratch (or "de novo") is typically time-consuming, data-intensive, and demanding of extensive expertise in health economics. Another option is to adapt an existing CEA to a new setting, using locally available data where possible.

There are a couple of prerequisites which would make model adaptation useful and efficient compared with de novo CEA. First, access to a model which is structurally suitable for the research question at hand is required. While there has been a recent increase in publicly available models, it may still be challenging to find a suitable and accessible model. Second,

it is critical to understand the components of the underlying economic evaluation in order to adapt it to the local setting, and available checklists or methods<sup>20</sup> for adaptation such as the Mullins checklist can be applied<sup>21</sup>. For example, a cost-utility analysis on adjuvant treatment for early breast cancer used the Mullins checklist to adapt a UK model to the South Africa setting, and found that both docetaxel and paclitaxel were predicted to be cost-effective as adjuvant treatments for early breast cancer in South Africa<sup>22</sup>.

Even with these prerequisites, it is possible that adapting a model may not be any faster or require any less capacity than a de novo CEA. This is because integrating local data into an existing model may be time consuming; the standard of care in India may be different from the model setting demanding a change of comparator; and general misalignment of the model setting with the local setting may lead researchers to conduct a CEA specific to India or adopt another approach anyway.

### **5.7.2 (Systematic) literature review and synthesis**

For topics which are well-studied in other countries, various approaches to literature review which synthesise relevant available evidence may be sufficient to inform the guidelines.

Evidence synthesized may include safety, efficacy, clinical-effectiveness, resource use, and cost-effectiveness/economic evidence (including appraisals from HTA agencies), depending on the type of intervention. For cancer medicines, detailed evidence may be available in all of these categories. For non-drug cancer interventions such as surgery or radiation therapy, available evidence may be limited to safety and efficacy. While the focus of this chapter is on economic evidence, it is important to note that it may only be feasible to make decisions for non-drug interventions based solely on safety and efficacy due to a dearth of economic evidence. This is common practice in some countries, for example, NICE UK undertakes this approach for surgeries or what it calls “Interventional Procedures”.

A systematic literature review<sup>23,24</sup> is the most comprehensive option and thoroughly identifies, evaluates, and summarizes all relevant empirical literature on a particular pre-defined topic through a transparent and reproducible search strategy with clearly defined inclusion and exclusion criteria. Evidence found in systematic reviews can either be summarized through narrative synthesis or if using statistical methods to summarize results, a meta-analysis.

Additional literature review techniques include narrative reviews (a qualitative synthesis of select studies); scoping reviews (identifies research gaps and opportunities for evidence synthesis)<sup>25</sup>; rapid reviews (an accelerated systematic review)<sup>26</sup>; and other non-systematic reviews. These can be used to more quickly extract key information from select literature.

Systematic literature review captures all available relevant empirical evidence on a given research question, but is also potentially a time consuming approach to evidence synthesis. The other alternative approaches may be conducted quite quickly, but represent a narrower evidence base, and thus come with the risk of increased uncertainty. All reviews have limitations related to

transferability of evidence to the Indian setting, and thus critical appraisal of the quality of the evidence must be undertaken. Any such literature reviews should be conducted by individuals experienced in evidence synthesis.

### 5.7.3 Price benchmarking

Another rapid approach that can be used as a supplement to literature review - but should not be used in isolation - is one of price benchmarking. This can illustrate how much more or less the price of a drug is in India compared with other benchmarked countries which have used economic evidence to inform their coverage and pricing decisions. The use of economic evidence in benchmark countries - preferably which use HTA - is key for price benchmarking, as the comparison of prices can then provide a proxy for whether an intervention is cost-effective in India based on whether and at what price it was deemed to be cost-effective elsewhere.

List prices used in previous price benchmarking analyses have come from the UK, US, Australia, New Zealand, and Thailand, but these are not the only countries from which list prices can be obtained. There are also global resources for list prices such as the MSH International Medical Products Price Guide<sup>27</sup>.

Benchmark list prices are adjusted by the ratio of Purchasing Power Parity (PPP)-adjusted gross domestic product in the country being analysed (e.g. India) and the source country (e.g. the UK) in order to standardise an 'apples to apples' comparison using the following formula:

$$\text{"Cost-effective" price in India} = \text{Country A price} \times \frac{\text{India PPP-adjusted GDP per capita}}{\text{Country A PPP-adjusted GDP per capita}}^{28}$$

The output of the analysis is a set of indicative maximum values at which the technology might be cost-effective in the analysed country.

Conducting such analyses are a quick way to identify 'low hanging fruits'; an extreme example would be if the adjusted price of a drug in India were more than the list price in the United States, then the price in India is probably far too high. However, benchmarking against other countries' prices will not reflect the local health system, clinical pathways, and medical practice. Notably, such analyses are also limited to list prices for *drugs* and not for other technologies (e.g. surgery, medical devices) given the heterogeneity of non-drug interventions, and these list prices do not account for inevitable confidential discounts which can be substantial. Furthermore, there is a need to ensure adequate comparison either between branded drugs or between biosimilars/generics, rather than comparing branded drugs in one context with biosimilars in another due to significant price differences. Thus, benchmarking should only be used as a 'sense check', and potentially a lever for price negotiations. Relatively little capacity is required to carry out price benchmarking analysis, as it only requires sourcing list prices and PPP-adjusted GDP per capita, and adjusting each value by a simple formula.

## 5.8 Using economic evidence to inform NCG guideline adoption decisions

Economic evidence is one important component in deciding whether to fund an intervention because it weighs the costs of the intervention in relation to the benefits it produces. This weighted benefit (the “ICER” from 5.5.1) can be used to inform coverage decisions using a variety of techniques<sup>29</sup>.

One option is to compare the ICER with a ‘threshold’ which represents the maximum financial investment a payer (eg AB-PMJAY) might pay for an additional unit of health<sup>30</sup>. For instance, the threshold in the UK is 20,000-30,000 GBP for most conditions (though other thresholds apply for different circumstances). Generally, if the ICER for a technology falls over that threshold, it is unlikely to be included in clinical guidelines. . Establishing a locally relevant threshold is challenging, but can be done using within-country data<sup>29</sup>. If the local threshold is not yet well established in practice, either crude global estimates of thresholds such as the 0.5 x GDP per capita WHO threshold or more locally tailored thresholds based on cross-country data can be used as a general guide in deciding whether to include evaluated interventions in updated clinical guidelines<sup>31,32</sup>.

Work is ongoing in India to determine the appropriate threshold(s). It is important to note that this chapter is meant to provide general guidance for the development of clinical practice guidelines to support the NCG, irrespective of the payer (private, PMJAY, or out-of-pocket). In time, local work on thresholds can be used to update decision rules and may even be aligned with India’s classification of ‘optional’, ‘optimal’, and ‘essential’.

Beyond thresholds, there are a few additional options for making funding decisions. A budget impact analysis (section 5.6) can be used as a supplement alongside a CEA and its ICER to determine whether an intervention is affordable in India, in addition to whether it is cost-effective. Alternatively, it is possible to review whether the intervention has been licensed for the given indication elsewhere, as well as whether it has been rejected for funding elsewhere. For example, if an intervention which was subject to economic evaluation by the UK NICE was rejected as not cost-effective or not effective, it may also be inappropriate for use elsewhere. Finally, a ‘league table’ approach can be used to compare the ICER of one intervention against others which are already covered<sup>33</sup>.

Importantly, other decision criteria for an intervention may be equally as important as economic evidence in the Indian context. These could include for example, ethics, social values, equity, and household financial impact<sup>34–36</sup>. Further details on this can be found in Chapter 6.

Given the combination of economic evidence and other factors, it is important that the evidence is reviewed and recommendations are made in a systematic and transparent way, which will also be discussed in Chapter 6.

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## Chapter 6. Making recommendations and writing the guideline

Making recommendations is a crucial part of the guideline development process because it involves the Guideline Development Group reaching decisions and coming to its final conclusions, taking into account a range of evidence from multiple sources and other factors that are specific to the Indian health context. This process is integral to writing the NCG guideline. This chapter describes how NCG guideline recommendations are agreed and formulated, and how the draft guideline documents are prepared.

### 6.1. Making recommendations

Chapters 4 and 5 described the use of existing guideline recommendations and how health economics inform NCG guideline recommendations. The NCG guideline may contain a combination of 'adopted' or 'adapted' recommendations from existing guidelines (Chapter 4) and 'de novo' recommendations informed by health economic analyses (Chapter 5). Irrespective of their provenance these recommendations are developed according to a structured approach that takes into account a wide range of scientific and social /contextual factors. Importantly, the credibility of the final recommendations is dependent on transparency of this decision making process.

#### 6.1.1. Factors involved in making recommendations

##### Quality of the evidence:

As noted in Chapter 5, the quality of the evidence relates to the degree of confidence in the estimates of effect and it is central to making a recommendation. The higher the quality of the evidence, the more confidence the GDG has in making a recommendation. However the quality of evidence is not the only factor that affects the decisions/judgement of the GDG.

##### Balancing benefits and harms

Moving from evidence to recommendations involves weighing up the magnitude and importance of the benefits and harms of an intervention, and also the potential for unintended consequences<sup>1</sup>. For example the GDG need to ensure that any benefit to the patient and also to the healthcare system outweighs, preferably by a substantial margin, any risks or harms associated with the recommended treatment/intervention. To make these judgments, the GDG needs to appreciate how substantial the expected benefits and adverse effects of the intervention are likely to be in practice. For example harms may range from clinical side effects to increased risks of developing long term health problems for individual patients. Equally, as seen in Chapter 5, a non-cost-effective intervention can displace other highly cost effective interventions/programmes that would benefit large populations.

Detailed tables of the clinical and economic evidence are essential when making such decisions. For examples of these tables in cancer guidelines see <https://www.nice.org.uk/guidance/ng101/evidence/evidence-review-a-surgery-to-the-breast-pdf-4904666606> (Pages 53-61) and <https://www.nice.org.uk/guidance/ng85/evidence/appendix-k-health-economics-evidence-profiles-pdf-170091398523> (accessed 22 February 2021)

### Equity

Health inequity has been defined as “differences in healthcare access or utilisation, quality of care or health outcomes that are considered avoidable and unfair, such as those associated with socioeconomic status, ethnicity or geographical region”<sup>2</sup>. It relates to socially or economically disadvantaged groups, clinical subgroups who experience different prevalence of disease or poorer health outcomes, inadequate access and poor quality medical care, such as gender, rurality, and ethnicity and who might be adversely affected by the recommendations<sup>3,4</sup>. Regardless of the care setting, there is potential for guideline recommendations to inadvertently create or increase health inequities by improving the health of the relatively health advantaged more readily than that of the relatively disadvantaged as results from studies may not always be relevant and applicable to the needs groups who are disadvantaged.

Oxman et al, propose a series of prompts to help guideline developers assess equity<sup>5</sup>. These are listed below:

- Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?
- Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?
- Are there different baseline conditions across groups or settings that affect the absolute impact of the intervention or the importance of the problem for disadvantaged groups or settings?

From a population perspective, equity involves making judgements about the fair and equitable distribution of scarce resources, often in the face of uncertain evidence. When making judgements about what health services should provide, the GDG should be able to explain what informs its judgements and how it took into consideration equity issues. The National Health and Medical Research (NHMRC) in Australia developed a framework for using equity issues and health evidence in clinical practice guidelines development<sup>6</sup>. One useful approach to addressing wider equity concerns, for example, is the use of equity checklists and criteria to be considered in conjunction with cost-effectiveness results<sup>7</sup>. An example of how a guideline committee considered equity factors in making recommendations is presented in Box 6.1

**Box 6.1. Example of equity factors discussed by the Committee on the NICE guideline: Brain tumours (primary) and brain metastases in adults NG99 (July 2018) (accessed 4 February 2021)**

<https://www.nice.org.uk/guidance/ng99/evidence/a-investigation-management-and-followup-of-glioma-pdf-4903134734> (Page 163)

The committee also discussed that people with physical disabilities might find it difficult to attend very frequent scanning, and that consideration should therefore be given to alternative modalities of assessment for these people. They did not make a specific recommendation on this point as the types of physical disability experienced by people with brain tumours were very variable, and in not referring specifically to disability the committee believed they would make it clear that all people with tumours should be offered appropriate follow up, regardless of the presence of a disability.

In making recommendations for NCG guidelines, the GDG should pay particular attention to equity issues regarding the “essential”, “optimal” or “optional” classification to ensure that disadvantaged groups receive at least the essential care they require (see Section 6.1.4).

### Feasibility of implementation

The GDG should judge to what extent it will be feasible to put the recommendations into practice in making the final recommendations. As noted in Chapter 3, the GDG will have already addressed these issues during the planning and scoping of the NCG guideline. Whilst making recommendations they will consider the extent of change in practice that will be needed to implement a recommendation, in NCG centres : local staffing, equipment, service organisation; at national level policy levers, information and service infrastructure, supplies and funding streams, and the possible need for a carefully controlled implementation with, for example, training programmes, gradual reorganisation of services and potential capital investment. These factors are especially relevant in deciding whether the recommendations should be “essential”, “optimal” or “optional” as they relate to the practicality of implementation with availability of expertise, infrastructure as well as costs and evidence (see section 6.1.4). The GDG should bear these parameters in mind whilst making recommendations and use their collective experience where appropriate. This should be documented in the guideline and in any resources to support implementation<sup>8</sup>.

### **6.1.2. Evidence to recommendations**

The GDG should keep a record of their discussions and explain clearly how they moved from the evidence to each recommendation, documenting how any issues influenced their decision-making. This should include the GDG’s view of the applicability of the evidence to people affected by the guideline and the health care setting where they will be used.

For each recommendation, the GDG should briefly explain their rationale for making the recommendations and how they think the recommendations may impact on practice or services. The Scottish Intercollegiate Network (SIGN) uses a ‘considered Judgement Form’ as a justification for its recommendations. [https://www.sign.ac.uk/assets/sign50\\_2019.pdf](https://www.sign.ac.uk/assets/sign50_2019.pdf) (Pages 34-36) (accessed 15 February 2021). The National Institute for Health and Care Excellence (NICE) guidelines contain sections that briefly explain why the committee made the recommendations and how they might affect practice. They link to details of the evidence and a full description of the committee's discussion. An example is presented in Box 6.2.

**Box 6.2. Example of rationale for making recommendations in the NICE colorectal cancer guideline NG 151 (29 January 2020)**

<https://www.nice.org.uk/guidance/ng151/chapter/Recommendations> (accessed 4 February 2021)

**Treatment for people with early rectal cancer [Recommendation 1.3.1](#)**

**Why the committee made the recommendations**

The committee agreed that it was not possible to recommend one treatment over another because of the low quality of the evidence and the limited amount of evidence available. The available evidence showed no clinically important differences between treatments and, in addition, for many of the outcomes specified in the protocol and a number of the comparisons no evidence was identified at all. However, based on their knowledge and experience, the committee noted that there are risks and benefits associated with each treatment option. They highlighted that while total mesorectal excision (TME) is a radical intervention and has more risks than the others, it is the only way to accurately stage lymph nodes and, by doing so, allow better treatment planning. Therefore, the committee recommended discussing the implications of each intervention with the person before making a choice.

**How the recommendations might affect practice**

Currently, endoscopic submucosal dissection (ESD) is not widely available in the UK. In centres where ESD is not already available, resources and time would be needed to provide this service, including purchasing equipment and training staff (although this would be a short-term cost). After this initial investment there will be minimal cost difference between ESD and alternatives. Transanal excision (TAE; including transanal minimally invasive surgery and transanal endoscopic microsurgery) and TME are current practice in the UK, so the recommendations will have a minimal effect for these interventions. However, the recommendations will allow for an informed discussion with patients so they are fully aware of the risks and benefits of each procedure.

Full details of the evidence and the committee's discussion are in [evidence review C1: treatment for early rectal cancer](#).

***Decision Frameworks (etDs)***

Recently, Evidence to Decision Frameworks (EtDs) have been used by Guideline Development Groups to help them make recommendations and coverage decisions in a structured and transparent way<sup>9</sup>. This approach does not replace the informal consensus approach the GDG uses or voting (when needed) to agree the final recommendations (Chapter 2), but it ensures that important factors that determine a decision (criteria) are considered to inform judgements about each criterion. It also helps the GDG structure the discussions and identify reasons for disagreement and it makes the reason for decisions transparent to guideline users or those affected by the decision. An adapted etD template is presented in Annexure 5. Irrespective of the framework used, the GDG should briefly justify their decision in a paragraph for each recommendation.

The GDG does not need to include *details* of discussion for all recommendations, but it should provide a record of discussion for recommendations or groups of recommendations that are controversial or contentious. For example, this may include recommendations where the evidence is weak, or where a recommendation would require major shifts in practice. There

should be a record of the controversial issues, how these were discussed and how they were resolved by the GDG. The final recommendations should be reached through a process of informal consensus but in the unlikely event the GDG is unable to reach agreement on controversial issues it may use voting (See Chapter 2, section 2.4.1).

### 6.1.3. Strength and classification of recommendations

The concept of the 'strength' of a recommendation is central to translating evidence into recommendations and to making *decisions*. It is generally accepted that some recommendations are stronger than others but different guidelines initiatives interpret and represent the concept in different ways. For example, NICE reflects the strength of the recommendation in the wording of recommendations, depending on the certainty of benefit from the evidence and whether others (guideline users) would reach similar conclusions<sup>10</sup>. SIGN uses a five-tier form of recommendations: [https://www.sign.ac.uk/assets/sign50\\_2019.pdf](https://www.sign.ac.uk/assets/sign50_2019.pdf) (Table 6.1) (accessed 15 February 2021).

There is no universally accepted approach to representing or classifying the strength of a recommendation but there is wide agreement that the factors described in 6.1.1. have an influence and therefore need to be considered by the GDG in formulating their recommendations and should be reported in the guideline.

### 6.1.4. Resource stratified recommendations

For NCG guidelines the strength of recommendations may be represented as “resource stratified recommendations” that take into account the clinical evidence, equity, costs and also implementation considerations. Earlier chapters mentioned that the NCG has proposed a categorization system for the NCG guideline recommendations into three groups defined as follows:

- **“Optional”**: would be recommendations that reflect the state of the art, and are based purely on the available evidence with no consideration for cost effectiveness.
- **“Optimal”** would be recommendations based on both evidence as well as cost effectiveness, but may not be widely available because of issues with expertise and infrastructure
- **“Essential”** would be recommendations based on the evidence, practicality (wide availability of expertise and infrastructure) as well as the cost or treatment and the value it offers. If centres do not have the capabilities to implement these, they should refer patients to a higher centre.

This classification is specifically designed for the implementation of NCG guidelines in India, and links to the Ayushman Bharat Insurance Scheme Health Benefit Packages. It has important implications for guiding practice that will inform pre-authorisation and claims processing where documentation will be required. As noted in Chapter 5, the GDG should discuss cost effectiveness and also the cost impact when formulating their recommendations. Resource stratified recommendations provide a framework for optimizing the use of AB-PMJAY resources that are available, allowing providers to deliver the best care possible with available resources and incrementally achieve demonstrable improvement in outcomes for all beneficiaries<sup>7,11</sup>.

### 6.1.5. Wording the recommendations

Recommendations should be clear, indicating the actions the clinicians (healthcare professionals) need to take, the information readers of the guideline need to know. They should reflect the PICO format and contain an indication of the quality of the evidence on which they are based. Outcomes are generally not mentioned. The language of each recommendation should be consistent across all recommendations in the guideline. Below is an example of a recommendation from the NICE guideline on Lung cancer: diagnosis and management [NG122] 28 March 2019 for: Combination treatment for non-small-cell lung cancer. <https://www.nice.org.uk/guidance/ng122/chapter/Recommendations#combination-treatment-for-non-small-cell-lung-cancer> (accessed 15 February 2021). Please note the wording of the recommendations may be summarized in the Quick Reference Guide for practical reasons (see section 6.2.2).

1.4.40: <i>For people with operable stage IIIA–N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider chemoradiotherapy with surgery.</i>

Each recommendation in the NCG guideline should also be annotated according to the NCG classification as ‘Essential’, ‘Optimal’ or ‘Optional’.

### 6.1.6. Research recommendations

In discussing the evidence and making recommendations the GDG is likely to identify areas in which there are uncertainties or in which robust evidence is lacking. To prioritise the most useful areas of research the GDG should prioritise up to 5 key recommendations for research that are likely to inform future decision-making in cancer care in India and where there are gaps in the current evidence base. These research recommendations can be taken up by national research programmes in India. The GDG should explain why they made the recommendation and how it may affect practice.

Below is an example of a research recommendation:

Which groups of people with early and locally advanced breast cancer would benefit from the use of adjuvant bisphosphonates?  <a href="https://www.nice.org.uk/guidance/ng101/chapter/Recommendations-for-research#key-recommendations-for-research">https://www.nice.org.uk/guidance/ng101/chapter/Recommendations-for-research#key-recommendations-for-research</a> (accessed 22 February 2021)
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## 6.2. Writing the guideline

The final guideline includes three separate documents that serve different purposes and different audiences:

- **The full guideline report** contains details of how the guideline was developed, the processes and methods that were used and that were covered in the previous chapters. It is a transparent record of the work of the GDG and it is essential in helping

guideline users understand how the recommendations were formed, their provenance, and how decisions were made in the context of the Indian care system.

- ***The Quick Reference Guide*** (or algorithm), similar to a patient pathway presents the recommendations in a format that is useful for healthcare practitioners at the point of care delivery
- ***The patient information leaflet*** provides information that is accessible to patients and informs them about the management of their condition

### 6.2.1. The full guideline report

The full guideline report contains all the recommendations, together with details of the methods used, including using existing guidelines (Chapter 4), the evidence underpinning the recommendations (chapters 3,4,5) and how final decisions were reached. This document is drafted by the NCG coordinators with input from the GDG Chair. Typically the report contains the following sections:

- *A summary section* containing:
  - all the recommendations, indicating if they are: “Optional”, “optimal” or “essential”
- *An introduction* describing:
  - Epidemiological data/the need for the guideline
  - The GDG membership and roles
  - The aim of the guideline
- *The scheduled update* of the guideline
- *A methods section* detailing:
  - How the guideline was planned and scoped ( See Chapter 3)
  - The clinical/review questions that were developed and prioritised (See Chapter 3)
  - For adopted or adapted recommendations from existing guidelines, the methods used and decisions made (Chapter 4 and sub-bullets 5 and 6 below)
  - For new clinical/ review questions and/or economic analyses: were formulated, the literature search strategy, how the evidence was reviewed and synthesised, including details of economic analysis if relevant (Chapter 5)
  - For groups of recommendations or controversial recommendations: An ‘evidence to recommendations’ section summarising the GDG discussions on the trade-off between benefits and harms, and consideration of equity, implementation factors and economic evidence for policy decisions (essential/optimal/optional) justifying the recommendation(s) and controversial areas discussed (Chapter 6).
- *Research recommendations*
- *References*
- *Annexures*, which should include:
  - The declarations of interest of each GDG member
  - The scoping form used in the guideline
  - For new clinical/ review questions, annexes with review protocol, details of search strategies, evidence tables
  - For Economic analyses, a protocol, analyses and results
  - Details of voting method (if used) and results



An example of a report for an adapted cancer guideline is available at: <https://ascopubs.org/doi/pdf/10.1200/JCO.2016.67.0182> (accessed 22 February 2021)

An example of the full guideline report (for de novo guidelines including economic analysis) is available at: <https://www.nice.org.uk/guidance/ng151/evidence/methods-pdf-7078330765>

### 6.2.2. The Quick Reference Guide (QRG) or algorithm

The aim of the Quick Reference Guide (QRG) is to encourage and promote the uptake of recommendations by health professionals. The QRG is a practical resource to use on a day-to-day basis and that includes all the final recommendations. It presents the NCG recommendations in a concise, easy-to-use format and utilizes a clinical pathway or algorithm of the clinical decisions described in the guideline where decision points are represented by boxes linked by arrows. The QRG is drafted by the coordinators and discussed with GDG members.

The QRG should contain an algorithm. It should be uncluttered: boxes should be limited to those defining the clinical problem and those representing a clear decision point. A logical sequence should be maintained so that each decision flows from the question that precedes it. It may be necessary to produce more than one algorithm if the recommendations cannot be summarised into one chart. The NCG guidelines are presented as algorithms/QRG.s on the NCG website.

<https://tmc.gov.in/ncg/index.php/guidelines/draft-guidelines-2020> (accessed 15 February 2021)

Other examples are available here:

[https://www.canceraustralia.gov.au/sites/default/files/publications/investigating-symptoms-lung-cancer-guide-all-health-professionals/pdf/investigating\\_symptoms\\_of\\_lung\\_cancer\\_-\\_the\\_guide.pdf](https://www.canceraustralia.gov.au/sites/default/files/publications/investigating-symptoms-lung-cancer-guide-all-health-professionals/pdf/investigating_symptoms_of_lung_cancer_-_the_guide.pdf) (accessed 22 February 2021)

### 6.2.3 The patient information leaflet

The current NCG guidelines do not have a patient information document. Future versions of NCG guidelines should include such a document as this would help patient and their families understand their condition and the proposed treatment and interventions better. This would also help the implementation of the guidelines in practice.

The patient information document summarises the recommendations in the NCG guideline in everyday language and is aimed at patients and the wider public<sup>12</sup>. It does not describe the condition or interventions in detail. This document allows patients to gain a better understanding of their condition. It also improves communication between health care professionals and patients. It is advisable to draft this document with input from patients' support groups who understand patient's perspective. For examples of patients leaflets or documents:

<https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/gynaecology/pi-ovarian-cancer.pdf>

<https://www.nccn.org/patients/guidelines/content/PDF/colon-patient.pdf>

<https://www.esmo.org/content/download/104831/1843409/1/ESMO-ACF-Multiple-Myeloma-Guide-for-Patients.pdf>



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## Chapter 7. Validating the NCG guideline

Quality assurance and consulting on the draft NCG guidelines provide an additional level of validation in their development process. Guidelines are subjected to internal quality control and external consultation with stakeholders and for comments on the content, validity, clarity, applicability and acceptability of the recommendations prior to their publication and dissemination. This chapter describes the validation process for draft NCG guidelines and how comments are addressed.

### 7.1. Quality assuring the draft guideline

Once the guideline documents have been drafted the GDG coordinators undertake a methodological screen of the guidelines. This internal quality screen helps to ensure that they have been developed according to the process and principles set out in the NCG guidelines manual. It also helps identify areas of the process that need clarification or more detailed explanation, especially on technical aspects of the guideline.

The coordinators can consult with the GDG chair and members to obtain more information or to discuss areas of uncertainty. The quality screen process should not change the recommendations made by the GDG. All questions and responses or discussion should be recorded as part of the quality trail

### 7.2. Consulting with the NCG Network and stakeholders

Public /stakeholder consultation is included in most international guideline standards. It allows the GDG to obtain valuable feedback on its draft guideline from the wider population. It can improve a guideline's quality, legitimacy, its acceptability to users and improve the adoption of its recommendations into policy and practice<sup>1,2</sup>. Importantly, consultation ensures that issues are taken into consideration from under-represented groups who may experience inequities due, for example to lack of inclusion in research, lack of access to health services or for other social/cultural/ personal reasons<sup>3</sup>. This in turn may lead to improved adherence to recommended treatments and proposed recommendations from wider groups. Stakeholder consultation can be beneficial for several reasons:

- Controversial issues can be identified and managed early before publication
- A wider range of views from target audiences, the public and patients can be incorporated into the guideline
- Gaps in the evidence can be identified
- The wording and presentation of the guideline can be improved or clarified
- Users can provide valuable feedback or suggestions about ways to effectively disseminate and implement the guideline or how recommendations might work in practice

#### 7.2.1 The consultation process

The draft version of the *full guideline* (guideline recommendations, how existing guidelines were used, evidence reviews, economic analyses and rationale for committee discussions) is posted on the NCG website for two months.

The NCG draft guidelines posted on the NCG website are open for consultation. This allows to capture the views from stakeholders (individuals or groups) that might not otherwise have been able to engage. Comments can be submitted by individuals or corporate, commercial, professional, policy makers, insurers or patients groups as well as NCG members (See Chapter 2 that outlined who the stakeholders are for NCG guidelines).

### 7.2.2. Optimising the stakeholder consultation process

When consulting with stakeholders It is helpful to inform them about the guideline development process and to set parameters for comments so respondents understand how their input can help improve the guidelines. This allows the GDG and coordinators manage comments and optimise the value of the process. For example NICE has an explanatory guide for the stakeholders and the public: <https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-information-for-stakeholders.pdf> (accessed 23 February 2021)

The National Health and Medical Research Council (NHMRC) in Australia proposes the following parameters to be considered in asking for comments during consultation<sup>4</sup>:

- Ask specific questions
- Describe what type of feedback will and will not be considered
- Describe the type of responses that will be accepted (e.g. comments, journal articles, guidelines, policies)
- Request that suggestions are concise and set a maximum word limit if necessary
- Set out the information in a logical order including line items, page numbers or structured forms to help with the collation process
- Set clear time frames and a firm deadline for submissions of evidence if appropriate

To help structure the submitted comments and uniformity it is helpful to provide a template to stakeholders<sup>5</sup>. Annexure 6 includes a comments form to help stakeholders understand what is required and to submit their responses and notes on how to use it .

### 7.2.3. Responding to stakeholder comments

Comments received from the stakeholders consultation are an essential part the quality assurance of the NCG guidelines and it is important that they should be responded to appropriately. The comments are compiled by the GDG coordinators and summarised by theme in a 'guideline consultation table' for consideration by the GDG. A short report highlighting areas of major concern is prepared by the coordinators

The GDG discusses the comments, preferably at a GDG meeting. If changes are made to the guideline recommendations as a result of the comments, this should be made clear in the response if no changes are made by providing clear reasons. Responses and changes are made with the agreement of the whole GDG before publication.

- A summary report highlighting the main comments that were received through consultation and responses will be posted on the NCG website

Any decisions made as a result of the consultation and the reasons for the decisions are recorded regardless of whether a change was made to the guideline or not. Any change should be reflected in the full guideline report and an audit trail of changes need to be kept. The summary report with main comments and responses should be published as an appendix in the full guideline report.

### 7.3. Additional reviews

In exceptional circumstances the GDG may decide to seek additional independent reviews or advice to help inform their decision before the guideline is published. This may be appropriate to address specific technical or equity issues, specialised clinical expertise, or areas of the guideline especially when the evidence is lacking.

For example,

- The GDG may have made broad recommendations that need to be reviewed by external clinical experts
- The GDG may seek review of economics analysis by external health economists to inform the categorization of some recommendations in the guideline as “essential”, “optimal” or “optional”

In future, the draft patient leaflet may be sent to non-professional reviewers in order to obtain comments from the patient’s perspective.

Regardless of the nature of these additional reviews, the GDG should make the final decisions on the recommendations. All external peer reviewers should complete a declaration of interests form (see Chapter 2).

Comments received from these additional reviews should be entered on a comments table and discussed by the whole GDG.

### 7.4. Publishing and updating the NCG guidelines

Once the GDG has finalised and edited the guideline documents these are published on the NCG website.

The NCG guidelines are formally reviewed/updated every two years following publication, unless new evidence emerges during that period that would require an earlier review. This evidence should be sufficiently strong to make it likely that one or more recommendations in the NCG guideline would need updating in a way that will change practice significantly. Examples of such evidence include data from randomised controlled trials, changes in licensing or warnings issued by licensing agencies, or major changes in costs.

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**ANNEXURE 1: Components of a scope**

Sections	Content*	Covered/notes
Title	The title of the guideline that reflects the content of the scope	
Topic	A short statement about the clinical topic covered in the guideline	
Background	Why the clinical guideline is needed, what is the clinical need (large variation in practice, poor outcomes)	
What is the Healthcare setting	Secondary and /or tertiary care, public and/or private hospitals; research centres, in all states of India	
Who is the guideline aimed at	Oncologists, oncology team (including clinicians, nurses, pharmacists, radiologists, pathologists, anaesthesiologists , palliative care experts) Other clinicians who are involved in the care of patients with suspected malignancies, post therapy continuation of care Stakeholders who would use the guidelines for claim authorization and reimbursements, quality monitoring Managers and policy makers	
Who is the focus of the guideline	Patients that will be covered (age, diagnosis) Patients that will not be covered ( e.g. patients with specific tumours, risks factors, family history)	
What will be covered	Key areas that the guideline intends to cover: types of interventions and treatments (e.g. Surgery to the breast, management of the positive axilla) What areas will not be included: (e.g. rehabilitation)	
What are the key clinical issues and clinical/review questions	These are the main issues identified and the draft clinical/review questions. The group should try to list the priorities and restrict the list of issues to a minimum at this stage, as it often expands during the development of the guideline. There may be up to 5-10 key clinical issues, each with between 2-4 questions (see 3.4) <b>Example:</b> <i>Key area:</i> breast surgery. <i>review question:</i> What is the optimal	

## ANNEXURE 1: Components of a scope

	tumour-free tissue margin in people with invasive breast cancer treated with breast conserving surgery or mastectomy?	
Economic aspects	Whether economic considerations are relevant; If the economic evidence will be reviewed and economic modelling undertaken, with an economic plan (see Chapter 5)	
Main outcomes	The outcomes that are considered when searching for and assessing the evidence (e.g. overall survival, treatment related morbidity)	
Equality/ethical considerations	Outline equality issues that have been identified, and how these have been addressed. (e.g. why any groups are excluded from the scope)	
Draft patient /care pathway	This is a draft algorithm of the main stages of the patient/care pathway. It helps to identify the main areas for improvement and define /draft the main clinical questions	
Regulations	The guideline may link to health regulations (for example health Insurance under AB_PMJAY) that might impact on its use. When this is the case the link should be noted in the scope.	
Links with other guidelines	List existing guidelines that will be considered in developing the guideline. This is from a quick sift of relevant guidelines from established national or international guideline programmes (see Chapter 4)	
Development timelines	Indicate planned dates for the development of the guideline	
References	List any references to: <ul style="list-style-type: none"> <li>existing guidelines</li> <li>Any link to how the guideline is developed (e.g the guidelines Manual)</li> </ul>	

\*Examples adapted from : Guideline scope (draft) NICE guideline (Update): Early and locally advanced breast cancer: diagnosis and management:

<https://www.nice.org.uk/guidance/ng101/documents/final-scope-2>



## **ANNEXURE 2:**

### **Excerpts from National Institute for Health and Care Excellence (NICE) Guideline scope Colorectal Cancer (update)**

<https://www.nice.org.uk/guidance/ng151/documents/final-scope> (accessed 20 January 2021)

This guideline will update and replace the NICE guideline on Colorectal cancer: diagnosis and management (CG131) and the NICE guideline on Improving outcomes in colorectal cancer CSG5. The guideline will be developed using the methods and processes outlined in Developing NICE guidelines: the manual. This guideline will also be used to update the NICE quality standard for Colorectal cancer (QS20).

#### **1. Why the update is needed**

New evidence that could affect recommendations was identified through the surveillance process. Topic experts, including those who helped to develop the existing guideline, advised NICE on whether areas should be updated or new areas added. Full details are set out in the surveillance review decision CG131 and CSG5.

#### **Why the guideline is needed**

##### **Key facts and figures**

Colorectal cancer (cancer of the colon or rectum, or “bowel cancer”) is the fourth most common cancer in the UK, with over 41,000 new cases diagnosed each year. Colorectal cancer affects both men and women. Risk factors include increasing age, genetics and family history (particularly syndromes such as familial adenomatous polyposis and Lynch syndrome), inflammatory bowel disease and other dietary and lifestyle factors.

Colorectal cancer is the second most common cause of cancer death in the UK, accounting for 10% of all deaths from cancer and approximately 16,000 deaths each year. Death rates have decreased by 42% overall since the early 1970s. Survival rates continue to improve. Overall, 76% of people diagnosed with bowel cancer live for at least 1 year, with 59% surviving at least 5 years and 57% for 10 years or more (2010-2011). Survival is linked to disease stage at presentation, with improved survival the earlier the disease is detected and treated.

#### **Current practice**

##### ***Diagnosis and staging***

Diagnosis of colorectal cancer is made using colonoscopy and confirmed histologically by biopsy. Standard practice is to stage all patients for distant metastatic disease. For those with rectal cancer, local tumour staging is done by MRI scan or transrectal ultrasound if MRI is contraindicated.

**Local disease** In colon cancer, standard treatment is to offer surgery to those who are fit enough. Locally-advanced colon cancer may be treated with neoadjuvant chemotherapy before surgery. Acute colonic stenting may be offered in cases of malignant large bowel obstruction.

Treating rectal cancer is more complex. Options include surgery alone, preoperative radiotherapy and preoperative chemoradiotherapy. Local excision of the tumour may not be needed after preoperative radiotherapy or chemoradiotherapy. A “watch and wait” approach with no resectional surgery is sometimes used if there is a complete clinical response after chemoradiotherapy.

### ***Metastatic disease***

Colorectal cancer is unusual among solid tumours in that metastatic spread to the liver can still be cured with combinations of surgery and chemotherapy. Recently, new chemotherapy drugs have been made available for metastatic colorectal cancer with the RAS wild-type mutation following a NICE technology appraisal. The chemotherapy pathways developed for the last NICE guideline need to be updated to recognise these changes.

## **2. Who the guideline is for**

People with suspected or diagnosed colorectal cancer or at risk of colorectal cancer due to Lynch syndrome, their families and carers and the public will be able to use the guideline to find out more about what NICE recommends, and help them make decisions. This guideline is for:

- Health professionals working in secondary care
- Cancer Alliances and cancer clinical networks
- Commissioners of colorectal cancer preventative
- diagnostic and treatment services (including Clinical Commissioning Groups and NHS England Specialised Commissioning)

*It may also be relevant for:*

- Healthcare professionals working in primary care
- People using colorectal cancer services, their family members and carers, and the public
- Private providers
- Voluntary sector organisations working with people with suspected or diagnosed colorectal cancer

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government and Northern Ireland Executive.

### ***Equality considerations***

NICE has carried out an equality impact assessment during scoping. The assessment:

- lists equality issues identified, and how they have been addressed
- explains why any groups are excluded from the scope.

The guideline will look at inequalities relating to:

- Older people with long term conditions/co-morbidities.

- The extent of staging for older people is an issue. This group often receive fewer investigations and have lower surgery rates

### **3. What the updated guideline will cover**

#### **3.1 Who is the focus?**

##### **Groups that will be covered**

- Adults (18 years and older) with newly diagnosed adenocarcinoma of the colon.  
Adults with newly diagnosed adenocarcinoma of the rectum.
- Adults with relapsed adenocarcinoma of the colon.
- Adults with relapsed adenocarcinoma of the rectum.
- Adults with clinical or genetic evidence of Lynch syndrome [hereditary nonpolyposis colorectal cancer (HNPCC)].

##### **Groups that will not be covered**

- People with anal cancer.
- Children and young people aged under 18 years.
- People with primary or secondary lymphoma of the colon and rectum.
- People with pure small cell carcinoma, or other pure neuroendocrine carcinomas, of the colon and rectum.
- People with neuroendocrine tumours of the colon and rectum.
- People with gastrointestinal stromal tumours (GIST) or sarcoma of the colon and rectum.
- People with squamous cells carcinoma of the rectum.
- People with appendiceal neoplasms.

#### **3.2. Settings**

##### **Settings that will be covered**

- All settings in which NHS commissioned care is provided.

#### **3.3. Activities, services or aspects of care**

##### **Key areas that will be covered in this update**

We will look at evidence in the areas below when developing this update. We will consider making new recommendations or updating existing recommendations in these areas only.

1. Prevention of colorectal cancer
  - a. Role of aspirin in the prevention of colorectal cancer in adults with clinical or genetic evidence of Lynch syndrome (hereditary nonpolyposis colorectal cancer)
2. Molecular biomarkers –
  - a. Use of molecular biomarkers to guide chemotherapy choice
3. Management of local disease
  - a. Rectal cancer
  - b. Colon cancer
  - c. Colonic stents for obstructing colon cancer

## ANNEXURE 2: Excerpts from NICE Guideline scope

4. Management of metastatic disease
  - a. Presenting with stage IV colorectal cancer
  - b. Methods for treating metastasis
5. Ongoing care and support
  - a. Follow-up after apparently curative resection
  - b. Management of post treatment sequelae
  - c. Information about managing bowel function
6. Service delivery
  - a. Surgical volumes and rectal cancer surgery

**Note** that guideline recommendations for medicines will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a medicines summary of product characteristics to inform decisions made with individual patients.

**Proposed outline for the guideline** The table below outlines all the areas that will be included in the guideline. It sets out what NICE plan to do for each area in this update.

<b>1.Prevention of colorectal cancer</b>	
NEW Role of aspirin in the prevention of colorectal cancer in adults with clinical or genetic evidence of Lynch syndrome (hereditary nonpolyposis colorectal cancer)	Review evidence: new area in the guideline
<b>2. Molecular biomarkers</b>	
NEW Use of molecular biomarkers in guiding chemotherapy choice	Review evidence: new area in the guideline
<b>3. Management of local disease</b> (some NEW areas focusing separately on rectal and colon cancer)	
Rectal cancer Colon cancer	Review evidence: update existing recommendations from guideline CG131, 1.2.1 – _1.2.1.8 (2011) and 1.2.3.1-1.2.4.4 (2011 & 2014) and 1.2.6.1- 1.2.7.1 (2011) as needed. Recommendations 1.2.5.1 – _1.2.5.3 are based on NICE technology appraisal 105. A link to the NICE Pathway where the TA appears will be added (2006)
	Recommendations 1.2.8.1-1.2.8.2 are based on NICE technology appraisal 100. A link to the NICE Pathway where the TA appears will be added (2006)

## ANNEXURE 2: Excerpts from NICE Guideline scope

Colonic stents for obstructing colon cancer	Review evidence: update existing recommendations from guideline CG131, 1.2.2.1 – _1.2.2.7 (2011 & 2014) as needed
<b>4. Management of metastatic disease</b>	
Presenting with stage IV colorectal cancer	Review evidence: update existing recommendations from guideline CG131, 1.3.1.1 – _1.3.1.2 (2011) as needed
Methods for treating metastasis	Review evidence: update existing recommendations from guideline CG131, 1.3.4.1 – _1.3.4.4 as needed. Recommendations 1.3.4.5 – _1.3.4.7 are based on NICE technology appraisal 61. A link to the NICE Pathway where the TA appears will be added (2003)
<b>5. Ongoing care and support</b>	
Follow-up after apparently curative resection	Review evidence: update existing recommendations from guideline CG131, 1.4.1.1 – _1.4.1.5 (2011) as needed
NEW Management of post treatment sequelae	Review evidence: new area in the guideline
Information about managing bowel function	Review evidence: update existing recommendations from guideline CG131, 1.4.2.1 – _1.4.2.5 (2011) as needed
<b>6. Service delivery</b>	
NEW Surgical volumes and rectal cancer surgery	Review evidence: new area in the guideline
<b>The following areas from CG131 will not be updated and will be removed from the guideline as there is no longer variation in practice</b>	
Diagnostic investigations	Remove existing recommendations from guideline CG131, 1.1.1.1 – _1.1.1.5 (2011)
Staging of colorectal cancer	Remove existing recommendations from guideline CG131, 1.1.2.1 – _1.1.2.4 (2011)
Imaging of hepatic metastases	Remove existing recommendation from guideline CG131, 1.3.2.1 (2011)
Imaging of extra-hepatic metastases	Remove existing recommendations from guideline CG131, 1.3.3.1 – _1.3.3.6 (2011)
<b>The following areas from CSG5 will not be updated either because they are already covered within scope of update of CG131 or other NICE guidelines or because they are no longer relevant to this guideline</b>	

## ANNEXURE 2: Excerpts from NICE Guideline scope

Patient centred care	Remove: refer to Patient experience in adult NHS services (2012) NICE guideline CG138
Access to appropriate services	Remove: refer to Suspected cancer: recognition and referral (2015) NICE guideline NG12
Multidisciplinary teams	Remove: see NHS England quality surveillance programme for colorectal cancer
Diagnosis	Remove: there is no longer variation in practice in relation to diagnosis so this section will not be updated and included in the guideline
Surgery and histopathology	Remove: refer to sections 3 and 4 of updated CG131 guideline for recommendations about surgery
Radiotherapy in primary disease	Remove: refer to section 3 of updated CG131 guideline for recommendations about radiotherapy in primary disease
Adjuvant chemotherapy	Remove: refer to section 3 of updated CG131 guideline for recommendations about adjuvant chemotherapy
Anal cancer	Remove: this is out of scope for this update
Follow-up	Remove: refer to section 5 of updated CG131 guideline for recommendations about follow-up
Recurrent and advanced disease	Remove: refer to section 4 of updated CG131 guideline for recommendations about recurrent and advanced disease
Palliative care	Remove: refer to Improving supportive and palliative care for adults with cancer CSG4

### Areas not covered by the guideline

1. Population screening.
2. Colonoscopic surveillance of high-risk groups, including people with a family history of colorectal cancer and people with inflammatory bowel disease.
3. Management of anal cancer.

### 3.4. Economic aspects

We will take economic aspects into account when making recommendations. For each review question (or key area in the scope) for which the evidence is being reviewed, we will develop an economic plan that states whether economic considerations are relevant, and if so whether this is an area that should be prioritised for economic modelling and analysis. We will review the economic evidence and carry out economic analyses, using and NHS and personal social services perspective, as appropriate.

### 3.5. Key issues and questions

While writing the scope for this updated guideline, we have identified the following key issues and key questions:

1. Prevention of colorectal cancer
  - a. How effective is aspirin in the prevention of colorectal cancer in adults with clinical or genetic evidence of Lynch syndrome (hereditary nonpolyposis colorectal cancer)?
2. Molecular biomarkers
  - a. Does the use of molecular biomarkers to guide chemotherapy choice improve outcomes for people with colorectal cancer?
3. Management of local disease
  - a. What is the most effective treatment for early rectal cancer?
  - b. Which people with early colon cancer can be treated with endoscopic resection alone?
  - c. Which people with localised colon cancer should receive preoperative chemotherapy?
  - d. What is the effectiveness of preoperative radiotherapy or chemo radiotherapy for rectal cancer?
  - e. Which people having neoadjuvant chemotherapy or chemoradiotherapy for rectal cancer do not need surgery?
  - f. What is the optimal surgery for rectal cancer?
  - g. What is the optimal duration of adjuvant chemotherapy for colorectal cancer?
  - h. What is the effectiveness of stenting compared with emergency surgery for suspected colorectal cancer causing acute large bowel obstruction?
  - i. What is the effectiveness of exenterative surgery for locally advanced or recurrent rectal cancer?
4. Management of metastatic disease
  - a. Does surgery for the asymptomatic primary tumour improve outcomes for people with incurable metastatic colorectal cancer?
  - b. What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer? In the:
    - i. Lung
    - ii. Liver
    - iii. Peritoneum

5. Ongoing care and support

- a. What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?
- b. What is the optimal management of post treatment sequelae (for example low anterior resection syndrome or chemotherapy related neurotoxicity)?
- c. What are the information needs of people during and after treatment of colorectal cancer?

6. Service delivery

- a. Is there a relationship between surgical volumes and outcomes in the treatment of rectal cancer (primary and recurrent disease)?

**3.6. Main outcomes**

The main outcomes that will be considered when searching for and assessing the evidence are:

1. Quality of life.
2. Overall survival.
3. Disease-free survival.
4. Progression free survival.
5. Treatment-related morbidity.
6. Treatment-related mortality.



# ANNEXURE 3: Evaluation sheet for recommendations from source guidelines

## ANNEXURE 3:

### Evaluation Sheet- Acceptability/applicability of recommendations from source guideline(s)

Adapted from: Guideline adaptation: a resource toolkit (version 2.0). Prepared by the ADAPTE Collaboration; 2009 . Available at <https://g-i-n.net/document-store/working-groups-documents/adaptation/resources/adapte-resource-toolkit-guideline-adaptation-2-0.pdf> (accessed 20 January 2021)

Recommendation 1	Guideline 1			comments	Guideline 2			comments
	Yes	unsure	No		Yes	unsure	No	
<b>Overall, the recommendation is scientifically and culturally acceptable</b>								
There is sufficient benefit of the intervention, compared with other available management								
The recommendation is compatible with the culture and values in India								
<b>Overall, the recommendation is applicable</b>								
The intervention is applicable to the patients in the health care setting in India								
The equipment/infrastructure is available in the health care setting in India								
The necessary clinical expertise is available in health care setting in India								
There are no or few constraints, policies or resources in the health care setting in India that would impede the implementation of the recommendation				If yes - please comment				

The process is repeated for each adapted recommendation

## **Annexure 4: From scoping to developing a protocol**

For each new research question, the GDG should ensure the draft PICO question that was developed as part of the scope (see Chapter 3) is well-defined and meets the requirements for the new analysis. Based on the assessment of evidence from existing guidelines (see Chapter 4), the GDG may want to refine or focus the review question accordingly. This may include, for example, specifying clinical subgroups, or the comparator.

Once the GDG has agreed the analytical approach and the research question is refined, a protocol for the analysis is developed. The protocol should specify:

- Background on the disease
- Available prevention/treatment options
- Adequate justification of why the analysis is needed
- The (refined) decision problem or 'PICO' including population and subgroups, intervention, relevant comparators, and outcomes to be addressed
- Methods for evidence synthesis including the search strategy, study selection/data extraction approach, quality assessment strategy, justification for search strategy
- Methods of analysis

## ANNEXURE 5: (EtD) for NCG decision making

### ANNEXURE 5: Criteria for Evidence to Decision (EtD) for GDG to make NCG recommendations

Adapted from: Moberg J, Oxman AD, Rosenbaum S, Schünemann HJ, Guyatt G, Flottorp S, Glenton C, Lewin S, Morelli A, Rada G, Alonso-Coello P, GRADE Working Group. The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health Res Policy Syst. 2018 May 29;16(1):45. doi: 10.1186/s12961-018-0320-2. PMID: 29843743; PMCID: PMC5975536. <https://health-policy-systems.biomedcentral.com/articles/10.1186/s12961-018-0320-2>

	Recommendation		Notes
Benefits & harms	How substantial are the desirable anticipated effects?		
	How substantial are the undesirable anticipated effects?		
Certainty of evidence	What is the overall certainty of the evidence of effects?		
Outcome importance	Is there important uncertainty about or variability in how patients/ people value the main outcomes?		
Balance	Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
Economic considerations	Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
	How large are the resource requirement costs for implementation?		
	What would be the impact on health equity?		
Acceptability	Is the intervention/recommendation acceptable to key stakeholders (patients, providers, decision makers)		
Feasibility	Is the recommended intervention feasible to implement?		

## ANNEXURE 6. Stakeholder comments form

### ANNEXURE 6. Stakeholder comments form

Adapted from the National Institute for Health and Clinical Excellence NICE : <https://www.nice.org.uk> (accessed 1 March 2021)

NCG Guideline title: xxx

Consultation on draft guideline – deadline for comments: xxx, email: xxx

Please read the checklist for submitting comments at the end of this form.

We would like your comments on the draft recommendations and any comments you may have on the full guideline report.

We would like to hear your views on these questions:

1. Which recommendations will have the biggest impact on practice and be challenging to implement? Please say why
2. [Insert any specific questions about the recommendations from the Developer, or delete if not needed]
3. How well do the recommendations: cover the issues in the scope, reflect what the evidence says, consider the needs of different groups (for example, children, minority ethnic groups)?
4. Do the recommendations use wording that is clear and easy to follow?
5. Are there any possible inconsistencies or disagreements about how the GDG interpreted and applied the evidence?
6. Is there any other evidence that should be included?
7. Do the research recommendations cover the important gaps in the evidence?
8. Which recommendations could have the biggest impact and which would be the most challenging to put into practice? - is this a repetition
9. What would help users overcome these challenges?

ANNEXURE 6. Stakeholder comments form

Comment number	Document (FGR for Full Guideline Report); (QRG for Quick Reference Guide); (PIL for Patient Information Leaflet) G (for General comment)	Page number Or <u>'general'</u> for comments on the whole document	Line number Or <u>'general'</u> for comments on the whole document	Comments
Example 1	FGR	14	35	We think that this recommendation may imply that .....
Example 2	QRG	16	45	Question: This recommendation will be challenging to implement in practice because .....
Example 3	General	General	General	Question 2: is this guideline expected to be used in all NCG centres?
Insert extra rows as needed				

Checklist for submitting comments:

- Use this comment form and submit it as a Word document
- Indicate which document you are commenting on by putting FGR for Full Guideline Report; QRG for Quick Reference Guide; PIL for Patient Information Leaflet or G for General comment
- Include page and line number for each comment
- If you are sending comments on behalf of a group or organisation combine all comments organisation into 1 response
- Type directly into the table
- Spell out any abbreviations you use
- For copyright reasons do not include attachments such as research articles, letters or leaflets
- Please provide the level of evidence to support your suggestion and the data on cost-effectiveness if applicable and available

A summary of comments received during consultations are published for openness and transparency, and to promote understanding of how recommendations are developed.