2. Methods

This document was developed using the standard operating procedures described in the *WHO handbook for guideline development, second edition (25)*. The process included: (i) identifying priority questions and outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of the evidence, (iv) formulation of recommendations and write-up of the guideline, and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations.

2.1 Contributors to the guideline

The groups involved in the development of the guideline are described below. The members of these groups are listed in Annex 2.

2.1.1 WHO Steering Group

The guideline development process was supervised by the WHO Steering Group, comprising staff members from four WHO departments: Maternal, Newborn, Child and Adolescent Health and Ageing; Mental Health and Substance Abuse; Nutrition and Food Safety; and Sexual and Reproductive Health and Research. The Steering Group drafted the initial scope of the guideline; identified priority questions in the "PICO" format (encompassing population, intervention, comparators and outcomes); prepared the guideline planning proposal; identified and invited systematic review teams, the guideline methodologist and members of the Guideline Development Group (GDG); supervised evidence retrieval, assessment and synthesis; organized the GDG meetings; prepared draft recommendations for the consideration of the GDG; compiled the final guideline document; and managed the guideline publication and dissemination.

2.1.2 Guideline Development Group (GDG)

The WHO Steering Group identified 25 external experts and stakeholders from the six WHO regions to form the GDG. Criteria included geographic representation, gender balance and no conflicts of interest. The final GDG was a diverse group of individuals with expertise in research, clinical practice, policy and programmes, guideline development methods and service delivery approaches, including patient and consumer representatives.

The GDG participated in a virtual scoping meeting with the Steering Group in December 2020, and provided input on the PICO questions and related details that had been drafted to guide the evidence reviews. The GDG members examined and interpreted the evidence, formulated the wording of the final recommendations and provided related remarks and considerations at virtual GDG meetings between November 2021 and January 2022. The GDG also reviewed and approved the final guideline document.

2.1.3 External Review Group (ERG)

The ERG included four technical experts and stakeholders with expertise and experience in the provision of care for the preterm or LBW infant. The group was geographically representative and gender balanced. The ERG peer-reviewed the draft guideline document after the GDG had approved it. They assessed and provided feedback on: factual errors; clarity of language; guideline decision-making processes; values and preferences of persons affected by the recommendations (including families, health workers, managers and policy-makers); and the implications for implementation. It was not within the remit of this group to change recommendations that had been formulated by the GDG.

2.1.4 Evidence Synthesis Team (EST)

The EST comprised the guideline methodologist, systematic review teams and members of the WHO Steering Group. Within the EST, there were two work streams, each addressing multiple domains (see section 2.4). The work streams initially prepared an overview of systematic reviews *(26)* and a review of what matters to families about the care of their preterm or LBW infant (see Table 1.1) *(14)*. They then appraised the quality of existing systematic reviews and commissioned new systematic reviews and structured searches. The EST members then reviewed each systematic review, prepared the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence-to-Decision (EtD) frameworks for each priority question and attended the GDG meetings.

2.1.5 External partners and observers

Representatives of the United Nations Children's Fund (UNICEF), Save the Children, the Bill & Melinda Gates Foundation, the International Pediatric Association (IPA) and the United States Agency for International Development (USAID) were invited to the GDG meetings as observers. These organizations are potential partners in the implementation of the guideline, as they have a history of collaboration with WHO in guideline dissemination and implementation. Observers were allowed to make comments during technical discussions at selected times during the GDG meetings. Observers did not participate in discussions on the final recommendations.

2.2 Declarations of interests by external contributors

In accordance with WHO procedures for declarations of interests (DOIs) *(27)*, all GDG, EST and ERG members and other external collaborators were asked to declare in writing any competing interests (whether academic, financial or other), using the standard WHO DOI form, before engaging in the guideline development process. All experts were instructed to notify the responsible technical officer of any change in relevant interests, in order to update and review potential conflicts of interest accordingly. In addition, the GDG members were requested to submit an electronic copy of their curriculum vitae.

The names and short curriculum vitae of the GDG members were published on the WHO website for public review and comment two weeks prior to the first GDG meeting.

The WHO Steering Group reviewed all DOI forms and curriculum vitae to determine whether any conflicts of interest existed. All findings from the DOI forms were managed in accordance with the WHO DOI guidelines on a case-by-case basis. To ensure consistency, the Steering Group applied the criteria for assessing the severity of a conflict of interest in the *WHO handbook for guideline development (25)*.

For this guideline, none of the declared interests were considered serious enough to pose any risk to the guideline development process or to reduce its credibility. Thus, all experts were only required to declare such interests at the first GDG meeting. At each subsequent GDG meeting, GDG and EST members and observers were required to share any new potential conflicts of interest with the group.

Some GDG members had performed primary research related to one or more of the guideline recommendations. In these cases, the experts were restricted from participating in discussions or formulating any recommendations related to that specific area of interest. There were no important conflicts of interest among the ERG members.

A summary of the GDG DOIs and how conflicts of interest were managed is provided in Annex 3.

2.3 Identifying priority questions and outcomes

At the scoping meeting, the GDG decided on the priority questions in the PICO format (population, intervention, comparators, outcomes), based on the following criteria:

- values and preferences of families as outlined in the systematic review, "What matters to families about the care of their preterm or low-birth-weight (LBW) infant" (see Table 1.1) *(14)*;
- public health importance;
- availability of new evidence; and
- questions not addressed by existing WHO guidelines or those identified for update.

The final scope of the guideline is presented in Table 1.2 and Figure 1.1. The PICO questions can be found in Web Annex A.

2.4 Evidence search, retrieval and review

The DECIDE approach (Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence) *(28)* was used to guide the evidence search, evidence synthesis and judgements by the EST, and the formulation of recommendations by the GDG. The DECIDE framework has nine core domains: benefits, harms, balance of effects, certainty, values, acceptability, resources, feasibility and equity (Table 2.2).

Table 2.2 Evidence-to-Decision (EtD) framework workstreams and methods

Work stream	Domain	Questions to be answered	Methods	Range of ratings
1	Benefits	How effective is the intervention?	Quantitative systematic reviews of effectiveness studies	Large, moderate, small, trivial, none, varies, unknown
	Harms	Are there important adverse events reported by the study from the intervention?	Quantitative systematic reviews of effectiveness studies	Large, moderate, small, trivial, none, varies, unknown
	Balance of effects	Does the balance between benefits and harms favour the intervention?	DECIDE approach[a]	Favours intervention, probably favours intervention, probably favours no intervention, favours no intervention, varies, unknown
	Certainty	What is the certainty of the effectiveness evidence?	GRADE[b] or GRADE-CERQual[c] assessment of the certainty of the body of evidence	Bias, imprecision, inconsistency, indirectness High, moderate, low, very low certainty
2	Values and preferences	Is there important variability in the values or preferences a family might have about the outcomes that would impact judgements about the balance of effects?	Qualitative systematic reviews of experimental, quasi-experimental and observational studies	Yes, probably yes, probably no, no, varies, unknown
	Acceptability	Is the intervention acceptable?	Qualitative systematic reviews of experimental, quasi-experimental and observational studies	Yes, probably yes, probably no, no, varies, unknown
	Resources	What resources are required and what are their costs?	Structured searches in resource, cost, feasibility and equity databases[d]	Negligible costs, low-to-moderate costs, large costs, varies, unknown
	Feasibility	What is the feasibility of the intervention? Can it be easily or conveniently implemented? Is the intervention acceptable and are the resources required achievable?	Structured searches in resource, cost, feasibility and equity databases[d]	Yes, probably yes, probably no, no, varies, unknown
	Equity	Can the intervention be provided in low-resource settings? Will the populations that need the intervention most receive it quickly and at low cost?	Structured searches in resource, cost, feasibility and equity databases[d]	Yes, probably yes, probably no, no, varies, unknown

[a] DECIDE = Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence *(28)*.

[b] GRADE = Grading of Recommendations Assessment, Development and Evaluation *(29)*.

[c] GRADE-CERQual = Confidence in the Evidence from Reviews of Qualitative Research *(30)*.

[d] Searches = Structured searches in UNICEF supply catalogue *(31)*, International Medical Products Price Guide *(32)* and the *WHO compendium of innovative health technologies for low-resource settings (33)*.

For effects (benefits and harms), evidence was derived from systematic reviews of randomized controlled trials (RCTs) where possible. If reviews of RCTs were not available, then systematic reviews of non-randomized studies of interventions were used. An overview of systematic reviews was compiled to identify all eligible systematic reviews that had been conducted in the last three years *(26)*. If systematic reviews were not available, they were commissioned from expert systematic review groups. All commissioned systematic reviews followed standard methods, including: a standard protocol published in advance; a clear PICO question; criteria for identification of studies, including search strategies for different bibliographic databases; methods for assessing risk of bias; and a data analysis plan. The protocols were reviewed and approved by members of the Steering Group. The language used to describe the evidence on effects was consistent with the Cochrane Effective Practice and Organisation of Care approach (EPOC) *(34)*. The GDG carefully considered the benefits and harms, the balance of effects, and the certainty of the evidence of effectiveness for each PICO question.

For values and acceptability, a systematic review on what matters to families about the care of their preterm or LBW infant was commissioned *(14)*. This systematic review also followed standard methods for qualitative reviews, including: a standard protocol published in advance; a clear research question; criteria for identification of studies, including search strategies for different bibliographic databases; methods for assessing quality; and a data analysis plan. The protocol was also reviewed and approved by members of the Steering Group.

For resources, feasibility and equity, structured searches were done using search terms from effectiveness reviews and guidance published in the last five years. Databases included: Excerpta Medica database (Embase), MEDLINE, UNICEF supply catalogue, International Medical Products Price Guide, and the *WHO compendium of innovative health technologies for low-resource settings (31-33,35,36)*.

This evidence was then compiled into a GRADE EtD framework for each priority question (see section 2.8).

2.5 Grading of the quality and certainty of the evidence

The GRADE approach was used to appraise the quality and certainty of the quantitative evidence for each priority question. GRADE is a standard systematic approach for developing and presenting summaries of evidence for clinical practice recommendations *(29)*. It uses standard tools, which are published online, including GRADE protocols and risk-of-bias tools for assessing randomized and non-randomized studies. A GRADE EtD framework is prepared for each quantitative outcome and the certainty of evidence is rated as "high", "moderate", "low" or "very low". The standard criteria for baseline GRADE ratings are that RCTs provide high-certainty evidence while non-randomized trials and observational studies provide low-certainty evidence. This baseline certainty rating is then downgraded based on characteristics of the study design: risk of bias, inconsistency, imprecision, indirectness and publication bias. Magnitude of effect and dose response allow upgrading of certainty for observational studies. Further details of the standard GRADE approach can be found online *(29)*. For this guideline, both the systematic review teams and the external guideline methodologist (members of the EST) independently performed grading of the quantitative evidence for each priority question and outcome. Consensus was reached through discussion among the methodologist and all members of the EST.

For the qualitative evidence, the reviews were appraised using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) tool *(30)*. This tool uses an approach that is similar conceptually to other GRADE tools and provides a transparent method for assessing and assigning the level of confidence that can be applied to qualitative evidence. The three domains are values, acceptability and feasibility, and each of them has four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question.

2.6 Review of evidence, decision-making and recommendations

The WHO Steering Group provided the EtD frameworks to the GDG members as soon as the documents had been drafted, and in advance of

the virtual GDG meetings. The GDG was asked to review and provide comments on the documents electronically before the GDG meetings where possible. At the virtual meetings, under the leadership of the GDG chairs, GDG members collectively reviewed the EtD frameworks, the draft recommendations and any comments received through preliminary feedback.

The meetings included: presentation of the evidence and EtD frameworks by the EST; consideration of each EtD domain; presentation of draft recommendations by the WHO Steering Group; deliberations on each recommendation; and discussion about justification, caveats or difficulties, implementation considerations and research gaps.

The purpose of the GDG meetings was to reach consensus on each recommendation, including its direction, strength and conditions, based on explicit consideration of all the domains within the EtD frameworks.

Recommendations were developed using WHO Guidelines Review Committee (GRC) criteria (Box 2.1) *(25)*:

Box 2.1 Approach for developing recommendations and good practice statements

The recommendation is:

A **"strong recommendation"** if the intervention is applicable to all preterm or low-birth-weight infants

- Strong recommendations should be phrased as "is recommended", "is not recommended", "should receive", "should not receive".

A **"conditional recommendation"** if the intervention is recommended under certain conditions, which could be shared decision-making, or in certain populations or settings

- Conditional recommendations should be phrased as "may be considered".

A **"good practice statement"** if the intervention is obviously beneficial and should be done in most circumstances, even though there is no, little or only very-low-certainty evidence

The recommendations should be accompanied by a description of the certainty of the body of evidence: "high", "moderate", "low", or "very low".

Source: WHO, 2014 *(25)*.

The final adoption of each recommendation was made by consensus, defined as the agreement by three quarters or more of the GDG. Consensus was reached for all recommendations in this guideline and there were no strong disagreements.

The GDG also identified important research gaps and implications. Where the certainty of available evidence was rated as low or very low, the GDG considered whether further research should be prioritized, based on whether the research would: contribute to improvements in care of the preterm or LBW infant; fill a knowledge gap that would inform new recommendations or change an existing recommendation; be likely to promote equity; and be feasible to implement. The research implications are summarized in Chapter 6 and full details can be found in Web Annex B.

2.7 Document preparation and peer review

Following the final GDG meeting, the WHO responsible technical officer prepared a draft of the full guideline document to accurately reflect the deliberations and decisions of the GDG. Other members of the WHO Steering Group provided comments on the draft document before it was sent electronically to the GDG members for review and further comment. Subsequently, the revised document was also sent to the ERG members for peer review. The Steering Group carefully evaluated the input of the GDG members and the ERG peer reviewers for inclusion in the guideline document and made revisions to the draft document as needed. Further modifications to the guideline were limited to corrections of factual errors and improvements in language to address any lack of clarity and to conform to WHO style.

2.8 Presentation of the recommendations and evidence

The recommendations are presented in the summary table in the executive summary of this guideline (Table 1). In Chapter 3, the recommendations and associated GDG remarks are presented at the start of the sections about each intervention, followed by background information and definitions, and a summary of the evidence for each recommendation. The evidence summaries present the evidence

on effectiveness (benefits and harms) of the interventions (sources and characteristics of the evidence, critical outcomes, other outcomes and subgroup analysis) followed by a summary of other evidence (values and acceptability, resources, feasibility and equity). Finally for each intervention, a summary of judgements is presented in a table, including justifications for the recommendation made (if any) and the EtD summary.

The GRADE data tables for each priority question are presented in the Web Supplement.[1] The GRADE tables contain the grading of: bias, inconsistency, indirectness, imprecision, number of participants, relative and absolute effect, risk difference and 95% confidence intervals. Further detail on methods can be found in the *WHO handbook for guideline development* and other documents *(25,29)*.

This guideline is also accompanied by three web annexes:[2]

- Web Annex A: Priority questions and outcomes
- Web Annex B: Detailed list of research implications
- Web Annex C: Changes from approved scope of guideline.

1 Available at: https://apps.who.int/iris/bitstream/handle/10665/363699/9789240060050-eng.pdf

2 Available at: https://apps.who.int/iris/bitstream/handle/10665/363698/9789240060043-eng.pdf