WHO/UNICEF guide for research on wasting and nutritional oedema in infants and children under 5 years

A global research priority agenda, guidance on evidence generation, and core outcome sets



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World Health Organization

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ISBN (WHO) 978-92-4-012566-7 (electronic version)
ISBN (WHO) 978-92-4-012567-4 (print version)

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Acknowledgements

The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) thank the many individuals who contributed to the development of this work, including the global research priority agenda, guidance on evidence generation, and core outcome sets on wasting and nutritional oedema in infants and children under 5 years of age.

Allison Daniel (consultant), Department of Nutrition and Food Safety, WHO headquarters, led the development and preparation of this work together with Jaden Bendabenda and Zita Weise Prinzo (Department of Nutrition and Food Safety, WHO headquarters). Kirrily de Polnay, Grace Funnell, and Minh Tram Le (UNICEF) gave guidance and contributed to the development of this guide for research. Marina Adrianopoli and Laurence Grummer-Strawn (Department of Nutrition and Food Safety, WHO headquarters) provided additional technical input and support during the process.

WHO and UNICEF also sincerely thank Celeste Naude and Michael McCaul, guideline methodologists, for their substantial contributions to the methods and conduct of this work and the content of this guide for research.

WHO and UNICEF gratefully acknowledge the UNICEF/WHO Technical Advisory Group (TAG) on Wasting and Nutritional Oedema (Acute Malnutrition) for their expert input, guidance, and engagement: Aida Alsaddeeq, Caroline Antoine, Ali Mohamed Elhag Arabi, James Berkley, Bindi Borg, Colleen Emary, Patrizia Fracassi, Kate Golden, Geraldine Honton, John Kabongo, Rozina Khalid, Praveen Kumar, Natasha Lelijveld (TAG co-chair), Nicolette Nabukeera Barungi, Terry Njeri Theuri, Temidayo Odebunmi, Sanne Sigh, and Indi Trehan (TAG co-chair).

Special thanks are extended to members of the research subworking group of the TAG for the external review of this guide for research with an emphasis on the guidance on evidence generation: Bernardette Cichon, Anna Heath, Suvi Kangas, Shuby Puthussery, Ritu Rana, Debbie Thompson, and Kirk Tickell. WHO and UNICEF thank additional external reviewers including Samou Diarra, Fekri Dureab, and Pearl Mallawaarachchi.

WHO and UNICEF also acknowledge the contributions of the WHO Ethics Review Committee to the guidance on evidence generation, and in particular thank G. Owen Schaefer, Ehsan Shamsi-Gooshki, and Vicki Xafis for their detailed inputs, coordinated by Lee-Anne Pascoe.

WHO Regional Advisors who provided input into this work: Abdul Baseer Qureshi, Fabio Da Silva Gomes, Leendert Nederveen, Padmini Angela De Silva, Laetitia Ouedraogo Nikiema, Florence Turyashemererwa, and Kremlin Wickramasinghe.

Financial support for content within this guide for research and for the TAG was provided by the Children's Investment Fund Foundation (CIFF), the Eleanor Crook Foundation (ECF), European Civil Protection and Humanitarian Aid Operations (ECHO), the Foreign, Commonwealth & Development Office of the United Kingdom of Great Britain and Northern Ireland (FCDO), and UNICEF.

A full list of contributors and their affiliations is provided in Annex 1.

Abbreviations

ACERs	average cost–effectiveness ratios
AEA	average expert agreement
CASP	Critical Appraisal Skills Programme
CHNRI	Child Health and Nutrition Research Initiative
CHW	community health worker
CI	confidence interval
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COS(s)	core outcome set(s)
COREQ	consolidated criteria for reporting qualitative research
DALYs	disability-adjusted life years
FAIR	Findable, Accessible, Interoperable, and Reusable (data principles)
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICERs	incremental cost–effectiveness ratios
IQR	interquartile range
MEURI	Monitored Emergency Use of Unregistered and Investigational Interventions
MQ-LNS	medium-quantity lipid-based nutrient supplement
MUAC	mid-upper arm circumference
ORS	oral rehydration solution
PROGRESS-Plus	Place of residence, Race/ethnicity, Occupation, Gender/sex, Religion, Education, Socioeconomic status, Social capital, plus other characteristics
QALYs	quality-adjusted life years
ReSoMal	Rehydration Solution for Malnourished children
RoB 2	Cochrane risk of bias tool for randomized trials, version 2
ROBINS-I V2	Risk Of Bias In Non-randomized Studies of Interventions, version 2
RPS	research priority score
RUTF	ready-to-use therapeutic food
SD	standard deviation
SFF	specially formulated food

SQ-LNS	small-quantity lipid-based nutrient supplement
TAG	Technical Advisory Group
TIDieR	Template for Intervention Description and Replication
UN	United Nations
UNICEF	United Nations Children's Fund
WAZ	weight-for-age z-score
WHO	World Health Organization
WHZ	weight-for-height z-score
WLZ	weight-for-length z-score

Executive summary

Introduction

The development process for the 2023 *WHO guideline on the prevention and management of wasting and nutritional oedema (acute malnutrition) in infants and children under 5 years* highlighted extensive evidence gaps that made it challenging for the Guideline Development Group to formulate recommendations for all guideline questions and interventions of interest.

Addressing wasting and nutritional oedema in infants and children requires prioritizing key areas for research, particularly considering the many evidence gaps and recent funding reductions. It is essential that research is reliable, robust, relevant, and well reported to inform decisions around wasting and nutritional oedema within and beyond WHO guidance. Furthermore, variability in outcome measurement and reporting highlights a need for core outcome sets for wasting and nutritional oedema to standardize reporting and synthesis of outcome data within and across studies.

Against this background, the World Health Organization (WHO), in collaboration with the United Nations Children's Fund (UNICEF), produced the following outputs, described in Figure 1:

A. A global research priority agenda for wasting and nutritional oedema

B. Guidance on evidence generation for interventions addressing wasting and nutritional oedema

C. Core outcome sets for effectiveness trials on wasting and nutritional oedema.

Figure 1. Outputs to support research and evidence generation

A. A global research priority agenda for wasting and nutritional oedema	B. Guidance on evidence generation for interventions addressing wasting and nutritional oedema	C. Core outcome sets for effectiveness trials on wasting and nutritional oedema
To guide researchers and others to focus their efforts on the most urgent evidence gaps	To strengthen the quality, relevance, and consistency of primary research evaluating interventions	To standardize reporting and synthesis of outcome data within and across studies

This document is structured around these three core outputs. Each output is presented within the sections detailing methods, outputs, and limitations.

Overall, this guide aims to support the generation of high-quality evidence to inform future WHO guidance for the prevention and management of wasting and nutritional oedema in infants and children. The target audience includes researchers, policy-makers, programme implementers, funders, and others involved in research in these populations.

A. A global research priority agenda for wasting and nutritional oedema

The World Health Organization has led the development of a comprehensive global research priority agenda for wasting and nutritional oedema in infants and children. The timeframe aligns with that of the Sustainable Development Goals and Global Nutrition Targets related to wasting and nutritional oedema, which have been extended to 2030. After 2030, WHO aims to make further updates to the research priority agenda.

In developing the research priority agenda, WHO used a Child Health and Nutrition Research Initiative (CHNRI) exercise, focusing on four populations and topics of interest:

1) Infants less than 6 months of age at risk of poor growth and development
2) Infants and children 6–59 months of age with severe wasting and/or nutritional oedema
3) Infants and children 6–59 months of age with moderate wasting
4) The prevention of wasting and nutritional oedema.

The CHNRI process comprised two surveys completed anonymously by experts involved in the prevention and management of wasting and nutritional oedema. The first survey was to ensure that the list of research questions was comprehensive and clear; the second was to score the questions based on their answerability, effectiveness, deliverability, and effect on equity.

The research questions that emerged focused largely on the delivery and effectiveness of interventions for the prevention and management of wasting and nutritional oedema, rather than on discovery or development. Top questions related to evaluating different ready-to-use therapeutic food protocol options with reducing quantities for severe wasting and nutritional oedema; determining reliable criteria for defining optimal growth in infants less than 6 months of age at risk of poor growth and development; assessing cost and cost–effectiveness of specially formulated foods and other dietary interventions for moderate wasting; and identifying effective interventions in humanitarian contexts to prevent wasting and nutritional oedema.

This research priority agenda will guide researchers, research institutes, funders, and policy-makers, among others, to focus their efforts on the most urgent evidence gaps for preventing and managing wasting and nutritional oedema towards 2030 and beyond.

B. Guidance on evidence generation for interventions addressing wasting and nutritional oedema

The purpose of this guidance on evidence generation is to strengthen the quality of primary research evaluating interventions for the prevention and management of wasting and nutritional oedema, and to ensure its relevance and consistency.

A version 0 draft of this guidance was produced by WHO, and reviewed by the UNICEF/WHO Technical Advisory Group (TAG) on Wasting and Nutritional Oedema (Acute Malnutrition) at the end of 2025. Members of the WHO team then refined the draft to version 0.1. WHO held a TAG consultation meeting, in collaboration with UNICEF, to discuss the draft and to agree the key messages through consensus. Further relevant points were then discussed and additional messages suggested, as appropriate, again requiring consensus. An updated version of the guidance on evidence generation was reviewed for final comments, with the TAG agreeing on the key messages being organized by type:

- Cross-cutting for all types of evidence generation;
- Effectiveness evidence generation, including evidence around the effects of interventions on health outcomes and cost–effectiveness of interventions;
- Contextual evidence generation, including evidence related to values, resource use (cost), equity, acceptability, and feasibility of interventions as well as implementation in practice.

Key messages across these three types of evidence generation emphasize the importance of ethical standards, as well as the conduct of high-quality randomized trials of interventions wherever appropriate; the use of diverse and inclusive selection criteria and settings; appropriate outcome measurement and follow-up; and contextual and implementation considerations to enhance the usefulness of evidence for decision-making.

Coordinated and robust evidence generation increases the usefulness and usability of evidence, particularly for syntheses, and contributes to future updates of WHO guidance, corresponding operational guidance, and national policies and protocols.

C. Core outcome sets for effectiveness trials on wasting and nutritional oedema

Informed by best practice methods of the Core Outcome Measures in Effectiveness Trials (COMET) Initiative, WHO developed six core outcome sets (COSs) for effectiveness trials around the prevention and management of wasting and nutritional oedema in infants and children.

Members of the Guideline Development Group and TAG were invited to participate in a Delphi process to establish these COSs. This involved scoring outcomes in two rounds of a survey, with consensus in the second round defined as a minimum of 70% of the expert panel giving a score of at least 7, and less than 15% scoring 3 or below.

Through this Delphi process, WHO developed a COS for each of the following:

1) Infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – interventions in inpatient settings;
2) Infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – interventions in outpatient/community settings;
3) Infants and children 6–59 months of age with severe wasting and/or nutritional oedema – interventions in inpatient settings;
4) Infants and children 6–59 months of age with severe wasting or nutritional oedema – interventions in outpatient/community settings;
5) Infants and children 6–59 months of age with moderate wasting – interventions in outpatient/community settings;
6) Prevention of wasting and nutritional oedema.

Outcome domains in some or all of the COSs include the following: mortality; clinical outcomes including deterioration and improvement requiring clinical judgement; breastfeeding indicators and weight change for infants less than 6 months of age; anthropometric outcomes; sustained recovery in trials with post-exit anthropometric data; and prevalence or incidence of wasting depending on the prevention intervention and trial design.

The COSs are intended to be used by researchers to ensure that, at a minimum, data for these critical outcomes are reported for all effectiveness trials in infants and children with wasting and nutritional oedema. Uptake of these COSs will strengthen primary research, evidence synthesis, future guidelines and related decision-making, including informing recommendations on wasting and nutritional oedema as updates to the WHO guidance.

1. Introduction

1.1 Background

The *WHO guideline on the prevention and management of wasting and nutritional oedema (acute malnutrition) in infants and children under 5 years*, published in 2023, addresses 16 guideline questions that were prioritized by the Guideline Development Group *(1)*. The guideline includes four populations and topics of focus: i) infants less than 6 months of age at risk of poor growth and development; ii) moderate wasting in infants and children 6–59 months of age; iii) severe wasting and nutritional oedema in infants and children 6–59 months of age; and iv) the prevention of wasting and nutritional oedema. The guideline has important implications for policy and practice aligning with the United Nations (UN) Global Action Plan on Child Wasting *(2)*.

As part of the Global Action Plan, the World Health Organization (WHO) agreed to coordinate and oversee the generation of new evidence and accelerate the process to update normative guidance, ensuring that guidelines reflect the latest evidence on identification and risk characterization, management, and prevention of wasting and nutritional oedema in infants and children *(2)*.

The development of the 2023 WHO guideline followed the *WHO handbook for guideline development, second edition (3)*. Central to trustworthy and transparent guideline development is GRADE (Grading of Recommendations, Assessment, Development, and Evaluations),[1] which offers a structured framework for assessing the certainty of evidence and decision-making, specifically for the development of guideline recommendations. GRADE is an approach for determining the certainty of evidence in evidence synthesis and provides a structured framework and transparent process of moving from evidence to decisions *(4)*.

The four levels of certainty of the evidence, based on GRADE, are summarized in Box 1. Higher certainty evidence reflects confidence that the true value of an estimate falls on one side of a threshold of interest or within a specified range of a decision-making threshold.

Box 1. Certainty of evidence based on GRADE *(4)*

- High certainty: There is high confidence that the true value of the estimate of interest is on one side of a threshold of interest or within a specific range.
- Moderate certainty: There is moderate confidence that the true value of the estimate of interest is on one side of a threshold of interest or within a certain range. The true value of the estimate may deviate slightly from the target of the certainty rating (i.e. may possibly fall in a different range).
- Low certainty: There is low confidence that the true value of the estimate of interest is at one side of a threshold of interest or within a certain range. The true value of the estimate may deviate from the target of the certainty rating (i.e. likely fall in a different range).
- Very low certainty: There is very low confidence that the true value of the estimate of interest is at one side of a threshold of interest or within a certain range. The true value of the estimate may deviate significantly from target of the certainty rating (i.e. probably fall in a different range.)

Certainty of evidence is considered when decisions are made about the strength of recommendations, with low and very low certainty evidence often leading to recommendations that are conditional as opposed to strong.[2] In addition to potential desirable and undesirable effects of an intervention and the certainty of the evidence, strength of recommendations is also influenced by values and resource-use (costs) for interventions *(4)*.

[1] Further information about GRADE can be found in the GRADE Book, which is the most comprehensive and up-to-date resource on the GRADE approach *(4)*.

[2] According to GRADE, strong recommendations are those for which there is a clear net benefit or net harm. They typically require high or moderate certainty. Conditional recommendations, on the other hand, are those for which the net benefit is very small, variable, or uncertain *(4)*.

Of note, several recommendations in the 2023 WHO guideline were underpinned by low or very low certainty evidence *(1)*. Examples of reasons for low or very low certainty evidence included few high-quality trials, heterogeneity in terms of intervention approaches and study methods, variability in the reporting of methods and outcomes, and paucity of data for populations and interventions of interest.

Some of the guideline questions prioritized for the WHO guideline lacked direct evidence for the Guideline Development Group to consider when formulating recommendations. Additional priority areas, beyond the guideline questions addressed in the 2023 WHO guideline, were not included in the list of 16 initial guideline questions. This list of guideline questions was generated based on the findings of four scoping reviews, current WHO guidance, inputs from collaborators and knowledge-users (WHO Member States and implementing organizations) and previous WHO technical consultation meetings (pre-prioritization stage) *(5)*.

Additional challenges encountered by the Guideline Development Group and systematic reviewers related to outcomes. Many outcomes reported by trials were not well defined, with large variations in definitions, criteria, and measurements being used across trials, such as for the outcome relapse *(6)*. Consequently, pooling and interpreting the body of evidence around effects on a specific prespecified outcome proved difficult.

Evidently, significant guidance gaps remain around the prevention and management of wasting and nutritional oedema *(5, 7–11)*. There is an urgent need for high-quality evidence that is directly relevant and usable for future updates to the 2023 WHO guideline, for both existing and new recommendations. Strengthened evidence can also support more effective and efficient implementation of interventions and best practices for the prevention and management of wasting and nutritional oedema across settings and contexts.

1.2 Purpose

The overall purpose of this guide is to support the generation of high-quality evidence to inform future WHO guidance for the prevention and management of wasting and nutritional oedema in infants and children. It was developed by WHO to provide a comprehensive global research priority agenda for wasting and nutritional oedema in infants and children under 5 years of age.

The guide builds on the 2023 WHO guideline, with plans to update it as new evidence emerges. The research priority agenda is global in scope and aims to address critical evidence gaps related to child health and health equity in these populations. The timeline of this agenda is through 2030, in line with the Sustainable Development Goals and the Global Nutrition Targets, which have been extended to 2030 *(12–14)*.

The World Health Organization has also produced guidance on evidence generation which aims to strengthen the quality of evidence,[3] relevance and consistency of primary research that evaluates interventions for the prevention and management of wasting and nutritional oedema in infants and children under 5 years of age.

Coordinated and robust evidence generation increases the likelihood that evidence can be synthesized and used to inform updates of WHO guidance, corresponding operational guidance, and national policies. It may also increase the certainty of evidence based on the GRADE approach,[4] which may contribute to stronger recommendations, and will help to inform considerations across the GRADE evidence-to-decision framework[5] outlined in Box 2 *(4, 15)*. Evidence-to-decision frameworks help decision-makers use evidence in a structured and transparent manner by considering important criteria for transparent and reproducible healthcare decision-making.

[3] Quality refers to the robustness of the evidence, where minimizing limitations in the design, execution, and reporting of research studies results in better quality evidence.

[4] The certainty of evidence about effects is assessed based on limitations in the design or execution of randomized trials, inconsistency, indirectness, imprecision, and dissemination bias *(4)*.

[5] The WHO-INTEGRATE evidence-to-decision framework is another framework that may be used for development of recommendations for public health and health system interventions.

Box 2. GRADE Evidence-to-Decision framework *(4, 15)*

- Problem: Is the problem a priority?
- Desirable effects: How substantial are the desirable anticipated effects?
- Undesirable effects: How substantial are the undesirable anticipated effects?
- Certainty of evidence: What is the overall certainty of the evidence of effects?
- Values: Is there important uncertainty or variability in how much people value the main outcomes?
- Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?
- Resources required: How large are the resource requirements (costs)?
- Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?
- Cost–effectiveness: Does the cost–effectiveness of the intervention favour the intervention or the comparison?
- Equity: What would be the impact on health equity?
- Acceptability: Is the intervention acceptable to key interest-holders?
- Feasibility: Is the intervention feasible to implement?

The guidance on evidence generation was developed in response to requests from researchers, governments and ministries of health, funders, and other interest holders[6] for clearer direction on how to generate evidence that is suitable for informing WHO recommendations[7] in these populations.

This is the first version of this type of guidance on evidence generation[8] for interventions addressing wasting and nutritional oedema and may be revised depending on its use and value.

The World Health Organization aimed to develop core outcome sets (COSs) related to the areas of focus in the 2023 WHO guideline on wasting and nutritional oedema through a Delphi process. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative defines COSs as "an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care". Importantly, using a COS does not imply that outcomes in a study should be restricted to those in the relevant COS. Rather, there is an expectation that data on the core outcomes will be collected and reported *(20)*.

Note that this guide for research is a normative product that aims to inform evidence generation which may be used for future updates to WHO guidance; it does not constitute WHO recommendations, policy positions, or standards.

[6] The term "interest holders" is used in this document due to the colonial connotations of the word "stakeholders" *(16)*.

[7] Research that does not fully adhere to the messages in this guide for research may still be used to inform WHO recommendations. Thus this guidance does not affect the inclusion of data and studies, as all relevant evidence should be included. Adherence to this guide for research does not guarantee inclusion for the purpose of WHO guidance if data and studies are not directly relevant to the guideline question at hand or do not meet pre-defined criteria for inclusion for a particular guideline question. The *WHO handbook for guidelines development: supplement: criteria for use of evidence to inform recommendations in World Health Organization guidelines* includes further detail about the use of evidence for WHO recommendations *(17)*.

[8] WHO has also developed guidance on evidence generation for new regimens for tuberculosis treatment and preventive treatment *(18, 19)*.

1.3 Scope and context

As with the 2023 WHO guideline, this guide for research takes a child health perspective rather than a public health approach – the health, growth, and development of children being at the forefront. This was a guiding principle of the 2023 WHO guideline *(11)*.

The guide also takes an explicit health equity lens with the goal of prioritizing research that can reduce health inequities and improve outcomes in disadvantaged children and their families.

The populations and topics of interest for the research priority agenda and guidance on evidence generation include:

i) infants less than 6 months of age at risk of poor growth and development;

ii) infants and children 6–59 months of age with severe wasting and/or nutritional oedema;

iii) infants and children 6–59 months of age with moderate wasting;

iv) the prevention of wasting and nutritional oedema.

For the guidance on evidence generation, there is a broad scope in terms of prevention and management interventions of interest[9] for which this guide for research may apply. Examples include:

- dietary management of wasting and nutritional oedema with approaches such as specially formulated foods, home diets and foods, etc;
- identification and management of wasting and nutritional oedema by community health workers;
- interventions to assess and manage breastfeeding/lactation difficulties;
- donor human milk and wet nursing, therapeutic milks, and other formulas provided in inpatient settings when needed;
- medical and nutritional support for mothers/caregivers; and
- cash programming interventions for prevention.

For the COSs specifically, the scope for infants aged less than 6 months was limited to infants with wasting and/or nutritional oedema and/or underweight only. Additionally, several of the above populations were subdivided by inpatient and outpatient/community settings. The populations and topics are as follows:

i) infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – interventions in inpatient settings;

ii) infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – interventions in outpatient/community settings;

iii) infants and children 6–59 months of age with severe wasting and/or nutritional oedema – interventions in inpatient settings;

iv) infants and children 6–59 months of age with severe wasting or nutritional oedema – interventions in outpatient/community settings;

v) infants and children 6–59 months of age with moderate wasting – interventions in outpatient/community settings; and

vi) the prevention of wasting and nutritional oedema.

[9] The guidance on evidence generation only focuses on intervention questions but is not specific to other types of questions such as diagnostic and prognostic questions.

1.4 Target audience

The target audience for this guide for research includes individuals and institutions involved in research in infants and children with, or at risk of, wasting and nutritional oedema, as well as funders of this research. Specifically, it is intended to be used by actors involved in research and practice around the prevention and management of wasting and nutritional oedema. Depending on the context, this may include:

- researchers and academic institutions
- programme implementers and evaluators
- clinicians and other health workers
- ministries of health and other relevant government entities
- nongovernmental organizations
- United Nations agencies
- institutional review boards, research ethics committees, or equivalent
- funders.

The World Health Organization and UNICEF strongly encourage collaboration between users of the guidance on evidence generation to ensure the greatest impact of evidence generated on interventions for the prevention and management of wasting and nutritional oedema.

This guide for research incorporates materials adapted from two papers: *A WHO global research priority agenda for wasting and nutritional oedema in infants and children under 5 years*; and *Development of core outcome sets for effectiveness trials focused on infants and children with wasting and nutritional oedema* (under Creative Commons License: CC BY 3.0 IGO).

2. Methods for developing the outputs

2.A A global research priority agenda for wasting and nutritional oedema

The World Health Organization coordinated the development of the global research priority agenda using a Child Health and Nutrition Research Initiative (CHNRI) exercise and in accordance with WHO guidance on research priority setting *(21–24)*. The CHNRI method is a systematic approach for setting research priorities, involving independent scoring of research questions following a predefined set of criteria *(21–23)*.

The World Health Organization aimed to invite a representative group of experts in the prevention and management of wasting and nutritional oedema to participate in the CHNRI process that involved two surveys. The experts included researchers, clinicians, policy-makers, programme implementers, and community partners with expertise in wasting and nutritional oedema.

As a first step, WHO consolidated all the research needs listed in the 2023 WHO guideline for each respective guideline question, which emerged from Guideline Development Group discussions throughout the guideline development process; these were then converted into questions. The research questions were categorized according to the four populations and topics described above, and further organized by research subdomains adapted for nutrition by Lelijveld et al *(25)*, including description, delivery, development, and discovery, as defined in Box 3.

Box 3. Research subdomains adapted for nutrition *(25)*

- Description: research to assess the burden of the problem, its determinants, and effectiveness of interventions to address the problem
- Delivery: research to improve how nutrition interventions are delivered, financed, and taken up
- Development: research to improve nutrition interventions that already exist
- Discovery: research that leads to innovation, i.e. entirely new nutrition interventions.

Between February and June 2025, potential participants were invited to complete the two surveys anonymously. Survey 1 was open for four weeks initially and extended for an additional two weeks; Survey 2 was open for six weeks and extended for an additional two weeks. Participants were allowed to participate in either or both surveys.

For each survey, basic descriptive information about participants was collected, including gender, location, expertise, and institution. Participants were asked to include their email address in Survey 1 if they would like to receive Survey 2, which was kept separate from all other survey results to maintain anonymity.

Survey 1 was undertaken to ensure the list of research questions was comprehensive and clear for scoring within Survey 2. For Survey 1, WHO shared the prepared list of research questions from the 2023 WHO guideline as described above. The objectives of Survey 1 were to:

i) identify potential research questions that would enhance the understanding of wasting and nutritional oedema and have the potential to inform policy and practice;

ii) ensure the list of research questions was comprehensive and clear; and

iii) collect expert feedback and suggestions for improvement.

The World Health Organization invited participants to add any additional priority research questions if they considered their additions to have the potential to enhance the understanding of wasting and nutritional oedema and/or could inform policy and practice. There was no limit to the number of research questions that could be proposed by participants.

Participants could also provide feedback or suggestions to improve the clarity or framing of any research questions, including specific suggestions for wording changes, additional context, or reorganization of the questions. Participants were asked to submit the survey even if they had no additional proposed research questions or comments.

The World Health Organization then reviewed the responses to revise the list of questions and to identify new questions for inclusion in the list. Only unique research questions that were within scope of the four populations and topics of interest were added to the list of questions for scoring in Survey 2. If proposals were not presented in question format, they were then converted into questions.

The objective of Survey 2 was to score research questions based on four CHNRI criteria: answerability, effectiveness, deliverability, and effect on equity *(21, 22)* as described in Box 4.

Box 4. CHNRI criteria for this research priority agenda

- Answerability: Research studies (qualitative and/or quantitative) to answer this research question are feasible and ethical, and can be completed by 2030
- Effectiveness: The findings of this research (qualitative and/or quantitative) could lead to effective interventions, programmes, or policies that improve child health
- Deliverability: The findings of this research (qualitative and/or quantitative) could lead to interventions, programmes, or policies that can realistically be implemented
- Effect on equity: The findings of this research (qualitative and/or quantitative) could contribute to reducing health inequities among disadvantaged children.

The rationale for selecting these criteria was that they reflected a focus on the child health perspective – a guiding principle in the development of the 2023 WHO guideline, described earlier *(11)*. These criteria may also lead to the generation of evidence that could inform WHO recommendations, including that around effectiveness and equity, as well as implementation of recommendations and good practice statements reflected in the deliverability criterion.

In Survey 2, participants were first asked to select the population(s) and topic(s) for which they wanted to score each research question based on their expertise. Participants were asked to read each research question carefully, reflecting on its importance and relevance to the identified population(s) and topic(s) of interest. They then scored the research questions according to the four CHNRI criteria above, with the options being “agree”; “neither agree nor disagree”; “disagree”; or “don’t know”.

In terms of scoring, “agree” was scored as 1 point; “neither agree nor disagree” as 0.5 points; and “disagree” as 0 points. “Don’t know” was not counted as a recorded score, with any “don’t know” responses omitted from the numerator and denominator. Note that all questions were mandatory if respondents agreed to score a certain population or topic; they could not advance if a question was left blank.

Research priority scores (RPSs), ranging from 0 to 100, were calculated for each research question by summing the scores assigned by respondents for each of the four equally weighted criteria and dividing by the number of responses to obtain a mean score for each criterion. The overall RPS was then calculated as the average of the four criterion-specific scores, reflecting the priority assigned to a research question. The top 20 research questions overall, based on RPSs, as well as the top 10 research questions within each of the four populations or topics based on RPSs, were displayed as priority areas for research. Average expert agreement (AEA) scores, which reflect the degree of agreement among respondents and complement the RPS by indicating the consistency of scoring across respondents, were calculated and presented alongside RPSs, with AEA scores closer to 100 indicating stronger agreement.

2.B Guidance on evidence generation for interventions addressing wasting and nutritional oedema

The process of developing the guidance on evidence generation involved several structured steps and followed WHO's guide for developing guidance on evidence generation *(26)*. This guide emphasizes that in some areas, "more detailed guidance is needed to enable the development of suitable trial/study designs aimed at producing relevant evidence for WHO's normative products such as guidelines" *(26)*.

The development process involved members of the UNICEF/WHO Technical Advisory Group (TAG) on Wasting and Nutritional Oedema (Acute Malnutrition). Prior to joining the TAG, all prospective members completed the standard WHO declaration of interests for experts form, which was reviewed by the UNICEF/WHO Secretariat. The TAG comprises 18 experts who advise UNICEF and WHO on a broad range of issues and topics related to wasting and nutritional oedema in infants and children.

The TAG was given an opportunity to review and provide feedback on a version 0 draft prepared by WHO in October/November 2025. This was sent to TAG members by email in a shared document in which the advisory group could add comments within a three-week period. All comments were reviewed by the WHO team who refined the document to version 0.1 in November 2025, incorporating TAG feedback as appropriate. This version was shared with the TAG one week prior to a hybrid TAG meeting in December 2025.

The United Nations Children's Fund and WHO then held a two-day TAG meeting to discuss the draft and to agree on the key messages through consensus. TAG members were asked to share any new declarations of interests at the meeting.

Following the meeting, the TAG was given an opportunity to review a revised version in its entirety. After this review, the document was shared with the research subworking group of the TAG as external reviewers. The subworking group also completed WHO declaration of interests forms which were reviewed by the WHO Steering Committee.

2.C Core outcome sets for effectiveness trials on wasting and nutritional oedema

The development of the COSs followed COMET best practice methods including eliciting views about critical outcomes in a consensus process with an expert panel *(20)*. WHO registered the project a priori in the COMET database.

The World Health Organization invited members of the Guideline Development Group for the 2023 WHO guideline and TAG to participate in the COS development process *(27)*. Some experts are members of both groups, bringing the total number of invited participants to 36. The experts are based across all six WHO regions and have research, clinical, programmatic, and policy experience related to wasting and nutritional oedema in diverse settings. Many participants are directly involved in the clinical care of infants and children with wasting and/or nutritional oedema. Participants did not necessarily have to be researchers to be able to contribute to this process. They were considered a single panel, and no further data were collected about the characteristics of the expert panel.

Initial outcome long lists were generated for each COS, starting with all outcomes prioritized for 13 effectiveness guideline questions for the 2023 WHO guideline, regardless of whether evidence was available for the outcome during guideline development. Specific outcomes within relevant broader domains that were identified in the 13 effectiveness systematic reviews commissioned for these guideline questions were also added. WHO carried over outcomes from one COS population to another if considered to be applicable to more than one population of interest, an example being child development.

The virtual Delphi process used to develop the six COSs consisted of two rounds of a survey followed by multiple consensus meetings. Round 1 involved scoring all outcomes in the initial long lists which were categorized by outcome domains for each COS. The expert panel scored outcomes based on a Likert scale

from 1 to 9. As with the outcome rating in the guideline development process, scores from 1 to 3 indicated "not important"; scores from 4 to 6 indicated "important but not critical"; and scores from 7 to 9, "critical importance" *(28, 29)*. Participants were able to select "don't know" if they felt unable to score any specific outcomes. For each COS, an open text box was provided for additional outcomes that participants could optionally suggest being included in the next round. All outcomes suggested during the first round of the survey were added to the second round.

For round 2, participants were sent their own results from round 1 and the overall results from the whole expert panel. The overall results were shared as means and standard deviations, and medians and interquartile ranges. Participants in the expert panel were invited in this round to re-score all outcomes based on the same Likert scale. They were asked to also score additional outcomes suggested by participants in the first round. There was a text box for each COS where participants could add questions or comments and give reasons for changing any scores between the first and second rounds. Additional outcomes could not be suggested in round 2.

The World Health Organization examined the results of round 2 to determine if there was consensus for the outcomes for each COS. Consensus for inclusion of an outcome was defined as a minimum of 70% of participants in the expert panel giving a score of at least 7 and less than 15% of participants scoring 3 or below *(30, 31)*.

After completion of the online survey, WHO scheduled multiple consensus meetings with the expert panel to finalize the six COSs. The first objective of the consensus meetings was to further narrow down the outcomes for each of the six COSs, aiming for a maximum of seven outcomes; the second objective was to agree on definitions, measures, and measurement of the final agreed outcomes included in the six sets.

For the first consensus meeting objective, each COS was shown separately using the same approach. The expert panel was presented with the list of outcomes that met consensus following the online survey. They were asked to first vote on each outcome using a three-point Likert scale using anonymous Zoom polling, with options being "not important", "important but not critical", and "critical importance". This approach has been shown to be effective in reducing the number of outcomes identified as critical and allowing for narrowing down the list *(32)*. If at least 70% of participants scored an outcome as critical during this poll, the outcome would move forward for possible inclusion in the COS. After this poll, regardless of the result, the expert panel was invited to share any arguments in favour of, or against, inclusion of the outcome in the COS, or any other important details related to the outcome. After discussion, and if deemed necessary based on whether there was discordance or ambiguity in the initial vote, participants were invited to vote again using the three-point Likert scale, with additional discussion following. If required, additional surveys using the same three-point Likert scale were used.

Upon completion of this process for each respective COS, there was time allowed for discussion about the entirety of the list of final outcomes to ensure agreement. Once all COSs were completed and the related nature of the sets considered, the final six COSs were displayed alongside each other for reflection and further discussion and shared with the expert panel following the meeting for final review.

There was also opportunity for input from the expert panel to agree on definitions/specific measures and measurement of outcomes that were included in the six COSs. WHO documented and consolidated guidance and key points about outcome definitions, measurement and reporting raised by participants throughout the consensus meetings, drawing on the recordings of the meetings. Participants also had the opportunity to review the consolidated guidance and key points after all the meetings were concluded.

3. Outputs to support research and evidence generation

3.A A global research priority agenda for wasting and nutritional oedema

Sixty-three participants across 28 countries completed Survey 1, and 50 participants across 23 countries completed Survey 2. There were participants from all six WHO regions for both surveys, almost one third being from the African Region. Few respondents were from the Western Pacific Region. Most respondents were researchers, making up 60.3% for Survey 1 and 78.0% for Survey 2. There was a high proportion of programme implementers for Survey 1 in particular (46.0%). In terms of types of organization, many participants were based at academic/research institutions (31.7% for Survey 1 and 42.0% for Survey 2) and nongovernmental organizations (38.1% for Survey 1, and 40.0% for Survey 2). Further participant information is provided in Table 1 with percentages rounded to the nearest whole number (which may not total 100% due to rounding).

Table 1. Participant information for each of the two surveys

	Survey 1, n (%)	Survey 2, n (%)
Gender		
Woman	35 (56%)	30 (60%)
Man	25 (40%)	19 (38%)
Non-binary	0	0
Other	0	0
Prefer not to answer	3 (5%)	1 (2%)
Primary location (WHO region)		
African Region (AFR)	20 (32%)	16 (32%)
Eastern Mediterranean Region (EMR)	6 (10%)	5 (10%)
European Region (EUR)	18 (29%)	11 (22%)
Region of the Americas (AMR)	10 (16%)	9 (18%)
South-East Asian Region (SEAR)	8 (13%)	7 (14%)
Western Pacific Region (WPR)	1 (2%)	2 (4%)
Role/profession/expertise[a]		
Researcher	38 (60%)	39 (78%)
Clinician	12 (19%)	6 (12%)
Policy-maker	3 (5%)	4 (8%)
Programme implementer	29 (46%)	12 (24%)
Community partner	2 (3%)	2 (4%)
Other	7 (11%)	7 (14%)
Organization type[a]		
Academic/research institution	20 (32%)	21 (42%)
Health facility	4 (6%)	5 (10%)
Health ministry	2 (3%)	0
United Nations agency	14 (22%)	5 (10%)
Nongovernmental organization	24 (38%)	20 (40%)
Community-based organization	1 (2%)	1 (2%)
Independent	4 (6%)	3 (6%)
Other	5 (8%)	6 (12%)

[a] Participants could select multiple options

An initial set of 87 research questions was identified during the guideline development process for inclusion in Survey 1, with participants proposing an additional 63 questions for inclusion in Survey 2. A total of 150 research questions across the four populations and topics (presented with their scores in Annex 2) were therefore included in Survey 2. The median number of responses, excluding blanks and "don't know" answers, was 33 (IQR 3). RPS ranged from 67.6 to 93.9; AEA ranged from 53.9 to 89.5. A strong correlation was evident between RPS as the predictor variable and AEA as the outcome variable, with linear regression showing a 1-point increase in RPS associated with a 1.28-point increase in AEA (95% CI: 1.22–1.34; $R^2 = 0.93$) (Figure 2). This correlation between RPS and AEA suggests that research questions receiving higher priority scores also tended to have greater consensus among respondents.

Figure 2. Relationship between research priority scores and average expert agreement



The top 20 research questions across the four populations and topics of interest based on RPSs are shown in Table 2. The top 10 research questions for each respective population and topic are shown in Tables 3 to 6. Further information can be found in an original paper published in BMJ Global Health *(24)*.

Table 2. Overall top 20 research questions across populations and topics

Ranking	Population or topic	Research question	Research subdomain	RPS	AEA
1	Infants and children 6–59 months of age with severe wasting and/or nutritional oedema	What is the effectiveness of different ready-to-use therapeutic food (RUTF) protocol options with reducing quantities compared to standard quantities?	Delivery	93.9	89.3
2	Infants and children 6–59 months of age with severe wasting and/or nutritional oedema	What are potential risk-targeted follow-up strategies of infants and children with severe wasting and/or nutritional oedema?	Delivery	93.6	89.5
3	Infants less than 6 months of age at risk of poor growth and development	What are reliable criteria for defining optimal growth in infants less than 6 months of age at risk of poor growth and development?	Description	92.8	86.3
4	Infants and children 6–59 months of age with moderate wasting	What are the cost and cost–effectiveness of specially formulated foods (SFFs) and other dietary interventions?	Delivery	92.5	88.7
5	Prevention of wasting and nutritional oedema	What are the most effective interventions in humanitarian contexts to prevent wasting and nutritional oedema?	Description	92.1	87.1
6	Infants and children 6–59 months of age with moderate wasting	What is the cost–effectiveness of integrating moderate wasting into the primary healthcare system (in places where moderate wasting is managed outside the health system)?	Delivery	92.0	89.3
7	Infants and children 6–59 months of age with severe wasting and/or nutritional oedema	What tools, support systems, etc. can be utilized to maximize effectiveness of community health workers (CHWs) management?	Delivery	91.9	86.8
8	Infants and children 6–59 months of age with moderate wasting	Which infants and children with moderate wasting should be prioritized for supplementation based on risk factors?	Delivery	91.8	87.4
9	Infants and children 6–59 months of age with severe wasting and/or nutritional oedema	What are the cost and cost–effectiveness of different quantities of RUTF?	Delivery	91.8	88.1
10	Infants and children 6–59 months of age with moderate wasting	Which interventions are effective to prevent relapse and improve long-term health and development outcomes in infants and children with moderate wasting?	Description	91.7	87.1
11	Prevention of wasting and nutritional oedema	What are the cost and cost–effectiveness of preventive interventions for wasting and nutritional oedema compared to each other?	Delivery	91.5	84.6
12	Infants less than 6 months of age at risk of poor growth and development	Which tools and strategies can health workers use to assess and manage simple breastfeeding problems effectively?	Delivery	91.5	85.7
13	Infants and children 6–59 months of age with moderate wasting	Would infants and children with moderate wasting who do not meet criteria for prioritization with SFFs in low-risk settings benefit from a dietary intervention?	Description	91.4	83.6

Ranking	Population or topic	Research question	Research subdomain	RPS	AEA
14	Infants less than 6 months of age at risk of poor growth and development	What intervention packages to support existing health staff, such as using peer counsellors for the assessment and management of breastfeeding/lactation difficulties, exist and how do they compare?	Development	91.2	84.7
15	Infants and children 6–59 months of age with moderate wasting	What are the most effective and cost–effective targeting strategies for the provision of SFFs for moderate wasting in humanitarian settings?	Delivery	90.7	83.7
16	Infants less than 6 months of age at risk of poor growth and development	What is the effectiveness of different types of formulas including F-75, diluted F-100, full-strength F-100, and infant formulas (potentially consider pre-term formulas if appropriate) as well as donor human milk in inpatient settings for infants less than 6 months of age at risk of poor growth and development, as well as those with severe wasting and/or nutritional oedema specifically?	Description	90.7	84.9
17	Infants and children 6–59 months of age with moderate wasting	What are the cost and cost–effectiveness of managing moderate wasting using available home foods in different contexts?	Delivery	90.6	85.0
18	Infants less than 6 months of age at risk of poor growth and development	How should infants less than 6 months of age at risk of poor growth and development who fail to respond to initial supported breastfeeding and clinical treatment be managed?	Delivery	90.5	83.2
19	Infants and children 6–59 months of age with severe wasting and/or nutritional oedema	Which interventions are effective to prevent relapse and improve long-term health and development outcomes in infants and children with severe wasting and/or nutritional oedema?	Description	90.1	84.8
20	Prevention of wasting and nutritional oedema	What is the cost–effectiveness of interventions for prevention of wasting and nutritional oedema, including logistics and implementation costs?	Delivery	90.0	83.3

AEA: average expert agreement; RPS: research priority score

Table 3. Top 10 research questions for infants less than 6 months of age at risk of poor growth and development

Ranking	Research question	Research subdomain	RPS					AEA
			A[a]	E[b]	D[c]	EE[d]	Overall	
1	What are reliable criteria for defining optimal growth in infants less than 6 months of age at risk of poor growth and development?	Description	91.4	94.1	90.0	95.6	92.8	86.3
2	Which tools and strategies can health workers use to assess and manage simple breastfeeding problems effectively?	Delivery	90.5	91.9	91.9	91.7	91.5	85.7
3	What intervention packages to support existing health staff, such as using peer counsellors for the assessment and management of breastfeeding/lactation difficulties exist and how do they compare?	Development	92.4	93.9	89.4	89.1	91.2	84.7
4	What is the effectiveness of different types of formulas including F-75, diluted F-100, full-strength F-100, and infant formulas (potentially consider pre-term formulas if appropriate) as well as donor human milk in inpatient settings for infants less than 6 months of age at risk of poor growth and development, as well as those with severe wasting and/or nutritional oedema specifically?	Description	94.6	94.4	90.5	83.3	90.7	84.9
5	How should infants less than 6 months of age at risk of poor growth and development who fail to respond to initial supported breastfeeding and clinical treatment be managed?	Delivery	91.2	94.1	91.4	85.3	90.5	83.2
6	What screening criteria should be used to detect infants less than 6 months of age at risk of poor growth and development in the community?	Description	94.7	88.2	89.5	82.9	88.8	82.2
7	Which packages of care are most effective at improving outcomes in infants less than 6 months of age at risk of poor growth and development and preventing wasting and nutritional oedema in these infants?	Development	90.3	89.2	87.5	88.2	88.8	84.6
8	What are the acceptability and existing practices around wet nursing, supplementary suckling technique, re-establishment of breastfeeding, etc.?	Description	90.3	88.9	90.0	84.7	88.5	81.8
9	What prioritization criteria can be used for infants less than 6 months of age at risk of poor growth and development if caseloads are high and resources limited?	Delivery	88.6	88.2	87.1	89.7	88.4	81.2
10	What are the priority medical and nutritional support and interventions for mothers/caregivers of infants less than 6 months of age at risk of poor growth and development?	Delivery	87.5	90.5	84.7	88.9	87.9	80.7

AEA: average expert agreement; RPS: research priority score. [a] Answerability; [b] Effectiveness; [c] Deliverability; [d] Effect on Equity

Table 4. Top 10 research questions for infants and children 6–59 months of age with severe wasting and/or nutritional oedema

Ranking	Research question	Research subdomain	RPS					AEA
			A[a]	E[b]	D[c]	EE[d]	Overall	
1	What is the effectiveness of different RUTF protocol options with reducing quantities compared to standard quantities?	Delivery	92.4	93.9	97.0	92.2	93.9	89.3
2	What are potential risk-targeted follow-up strategies of infants and children with severe wasting and/or nutritional oedema?	Delivery	96.9	95.5	88.3	95.5	93.6	89.5
3	What tools, support systems, etc. can be utilized to maximize effectiveness of CHW management?	Delivery	90.9	92.2	92.2	92.2	91.9	86.8
4	What are the cost and cost–effectiveness of different quantities of RUTF?	Delivery	95.6	92.6	92.6	86.4	91.8	88.1
5	Which interventions are effective to prevent relapse and improve long-term health and development outcomes in infants and children with severe wasting and/or nutritional oedema?	Description	87.5	95.6	87.9	89.4	90.1	84.8
6	What chronic conditions are associated with non-response or treatment failure in infants and children with severe wasting and/or nutritional oedema?	Description	92.6	89.7	81.8	92.6	89.2	82.1
7	What are the cost and cost–effectiveness of alternative RUTF formulations in different settings?	Delivery	92.2	92.4	85.9	85.4	89.0	80.4
8	What are the risk factors (individual, household, community, programme-level) for relapse to severe wasting and/or nutritional oedema?	Description	92.4	86.4	84.4	92.4	88.9	83.2
9	What is the effectiveness of CHWs in management of severe wasting and/or nutritional oedema throughout the care pathway?	Delivery	84.8	89.4	89.1	90.9	88.6	80.9
10	What is the cost–effectiveness of CHWs for management of severe wasting and/or nutritional oedema and the impacts of this approach on coverage and other services?	Delivery	84.8	89.4	89.1	90.9	88.6	80.9

AEA: average expert agreement; RPS: research priority score [a] Answerability; [b] Effectiveness; [c] Deliverability; [d] Effect on Equity; RUTF: ready-to-use therapeutic food; CHW: community health worker

Table 5. Top 10 research questions for infants and children 6–59 months of age with moderate wasting

Ranking	Research question	Research subdomain	RPS					AEA
			A[a]	E[b]	D[c]	EE[d]	Overall	
1	What are the cost and cost–effectiveness of SFFs and other dietary interventions?	Delivery	98.5	94.1	89.7	87.5	92.5	88.7
2	What is the cost–effectiveness of integrating moderate wasting into the primary healthcare system (in places where moderate wasting is managed outside the health system)?	Delivery	93.9	93.9	87.9	92.2	92.0	89.3
3	Which infants and children with moderate wasting should be prioritized for supplementation based on risk factors?	Delivery	92.6	97.1	89.7	87.9	91.8	87.4
4	Which interventions are effective to prevent relapse and improve long-term health and development outcomes in infants and children with moderate wasting?	Description	89.4	98.5	86.4	92.4	91.7	87.1
5	Would infants and children with moderate wasting who do not meet criteria for prioritization with SFFs in low-risk settings benefit from a dietary intervention?	Description	95.6	95.6	83.8	90.6	91.4	83.6
6	What are the most effective and cost–effective targeting strategies for the provision of SFFs for moderate wasting in humanitarian settings?	Delivery	86.8	94.1	91.2	90.9	90.7	83.7
7	What are the cost and cost–effectiveness of managing moderate wasting using available home foods in different contexts?	Delivery	91.2	91.2	91.2	89.1	90.6	85.0
8	What is the effectiveness of CHWs in management of moderate wasting throughout the care pathway?	Delivery	87.9	92.4	86.4	92.4	89.8	84.8
9	What are the risk factors (individual, household, community, programme-level) for relapse to moderate wasting?	Description	95.6	89.7	86.8	84.8	89.2	81.4
10	What tools, support systems, etc. can be utilized to maximize effectiveness of CHW management?	Delivery	87.5	89.1	84.8	93.5	88.6	82.0

AEA: average expert agreement; RPS: research priority score. [a] Answerability; [b] Effectiveness; [c] Deliverability; [d] Effect on Equity; SFFs: specially formulated foods; CHWs: community health workers

Table 6. Top 10 research questions for prevention of wasting and nutritional oedema

Ranking	Research question	Research subdomain	RPS					AEA
			A[a]	E[b]	D[c]	EE[d]	Overall	
1	What are the most effective interventions in humanitarian contexts to prevent wasting and nutritional oedema?	Description	85.7	97.1	88.6	97.0	92.1	87.1
2	What are the cost and cost–effectiveness of preventive interventions for wasting and nutritional oedema compared to each other?	Delivery	90.6	92.2	87.9	95.5	91.5	84.6
3	What is the cost–effectiveness of interventions for prevention of wasting and nutritional oedema, including logistics and implementation costs?	Delivery	92.6	88.2	89.7	89.4	90.0	83.3
4	What are the most effective and cost–effective platforms or services to implement food-based interventions for prevention of wasting and nutritional oedema?	Delivery	89.7	91.2	87.9	89.1	89.5	81.2
5	What is the potential role of cash programming in prevention of wasting and nutritional oedema, in isolation or in combination with other interventions?	Development	95.6	89.7	84.3	88.2	89.5	83.3
6	What low-cost and scalable livelihood initiatives can build resilience against wasting and nutritional oedema?	Development	83.9	90.3	88.3	93.3	89.0	82.0
7	What is the effectiveness of other types of prevention interventions apart from small-quantity lipid-based nutrient supplements (SQ-LNS) and medium-quantity lipid-based nutrient supplements (MQ-LNS) for prevention of wasting and nutritional oedema?	Description	89.4	94.1	84.8	85.9	88.6	77.9
8	What are the optimal quantity, duration and timing of food-based interventions for prevention of wasting and nutritional oedema?	Delivery	89.7	92.6	83.8	83.3	87.4	80.7
9	What are the direct, indirect, and opportunity costs to families of food-based interventions for prevention of wasting and nutritional oedema?	Delivery	86.4	85.3	85.3	89.4	86.6	74.7
10	What are the potential impacts of maternal interventions in the context of prevention of wasting and nutritional oedema?	Description	87.9	88.2	81.4	86.4	86.0	78.6

AEA: average expert agreement; RPS: research priority score [a] Answerability; [b] Effectiveness; [c] Deliverability; [d] Effect on Equity

3.B Guidance on evidence generation for interventions addressing wasting and nutritional oedema

This guidance on evidence generation was developed through an iterative process involving multiple rounds of review and a consensus process with the TAG. A version 0 draft was reviewed in October/November 2025 and refined to version 0.1 after feedback from the TAG. It was then discussed during a TAG meeting in December 2025 when consensus on all key messages was reached. A further revision of the document was then shared with TAG members in March 2026 for final review.

This guidance on evidence generation is organized by three types of evidence generation with a set of key messages applicable to each, as outlined in Box 5. The key messages for these types of evidence generation are summarized in Box 6, with further detail provided in the content following.

Box 5. Types of evidence generation included in this guidance

- Cross-cutting for all types of evidence generation
- Effectiveness evidence generation, including evidence around the effects of interventions on health outcomes and cost–effectiveness of interventions
- Contextual evidence generation, including evidence related to values, resource-use (cost), equity, acceptability, and feasibility of interventions as well as implementation in practice.

Box 6. Summary of key messages for the three types of evidence generation

- Cross-cutting for all types of evidence generation:
  - Foster inclusion, participation, and collaborative partnerships
  - Uphold ethical standards in obtaining evidence.
- Effectiveness evidence generation:
  - Design and conduct high-quality randomized trials of interventions whenever appropriate
  - Use diverse and inclusive selection criteria in terms of populations of infants and children
  - Conduct studies in diverse research settings and contexts
  - Clearly outline specifications of interventions and their delivery
  - Include relevant comparison arms based on current recommendations or standard of care
  - Measure and report outcomes included in core outcome sets
  - Report on adverse events consistently and comprehensively
  - Assess outcomes at appropriate timepoints with sufficient follow-up duration
  - Ensure that sample sizes are adequate for precise estimates around relevant outcomes
  - Provide detailed analyses for each outcome with data disaggregated by subgroup
  - Perform cost–effectiveness evaluations in relation to relevant outcomes
  - Make protocols and methods publicly available
  - Develop and follow a data management and sharing plan.
- Contextual evidence generation:
  - Aim to understand the values placed on key outcomes and their relative importance
  - Assess the impact of interventions on health equity
  - Evaluate the acceptability of interventions from multiple perspectives
  - Determine the feasibility, potential for scale-up, and coverage of interventions
  - Obtain and present data on resource use from different costing perspectives
  - Share detailed information about how interventions are implemented within programmes
  - Document any unintended positive and negative consequences resulting from implementing an intervention.

All studies in infants and children at risk of poor growth and development or with severe wasting and/or nutritional oedema should apply the cross-cutting key messages. However, not all studies are expected to generate both effectiveness and contextual evidence. Where feasible, researchers are encouraged to incorporate multiple types of evidence, for example with mixed-methods study designs or trials that incorporate implementation research, which can strengthen the relevance, utility, and applicability of findings.

Not all key messages described below will be applicable to every study. Researchers should apply methodological considerations that are relevant to the design and purpose of the study.

Cross-cutting for all types of evidence generation

Foster inclusion, participation, and collaborative partnerships

Research and interventions for risk of poor growth and development, wasting, and nutritional oedema should be designed and carried out with the inclusion of mothers/caregivers, families, communities and community representatives/leaders, health workers, and/or other relevant interest holders. This follows the principle of "nothing about us without us", with "us" referring particularly to mothers/caregivers and families of infants and children affected by wasting and nutritional oedema, thereby ensuring the social value of the research.

Those conducting the research should be cognizant of power imbalances and should promote equitable partnerships and meaningful participation. Co-production of evidence, for example through approaches such as participatory action research, can ensure that research is ethical, relevant, and responsive to priorities and values of those affected by the research and/or interventions. Understanding the perspectives of interest holders can also inform WHO recommendations in terms of values, equity, acceptability, and feasibility, as described later in this guidance. It is also likely to increase trust and confidence related to the research *(33)*.

In addition, ministries of health and other relevant ministries should be actively involved throughout the research process to ensure alignment with national priorities, sustainability, and uptake, and to support the translation of evidence into practice. Furthermore, relevant national coordination and technical bodies such as national nutrition working groups should be consulted and engaged.

At the conclusion of the research, findings should also be disseminated to interest holders including mothers/caregivers, families, communities, and others through well-planned knowledge translation strategies to ensure accountability and transparency.

Uphold ethical standards in obtaining evidence

Universal to all studies, study protocols should be reviewed, where required, by institutional review boards, research ethics committees, or equivalent, in the settings where the research is conducted, as well as from other responsible institutions to which researchers are affiliated. Protocols should comply with local regulations and laws.

It is critical to obtain informed consent, ensuring that participants including mothers/caregivers fully understand the study and its implications. Measures should be put in place to safeguard confidentiality and ensure appropriate data protection.

Those conducting research on the prevention and management of wasting and nutritional oedema should also consider specific ethical issues that pertain to mothers/caregivers and infants and children at higher risk of poorer outcomes and those in high-risk contexts.[10] These risks may include individual child factors as

[10] As per the 2023 WHO guideline, high-risk contexts (where there is a recent or ongoing humanitarian crisis) include those where the majority of the population is affected by any of the following characteristics/circumstances: high rates of food insecurity; and/or poor water quality and sanitation (or poor water, sanitation and hygiene (WASH) indicators); and/or low-income status/low socioeconomic status; and/or high incidence/prevalence of wasting and/or nutritional oedema, which could be seasonal *(1)*.

well as social and contextual factors such as the death of the mother, low socioeconomic status, etc., which may increase risk of harm. It is important to also recognize intersecting factors like gender, migration status, disability, and poverty, and how these can shape access and outcomes. In settings with a recent or ongoing humanitarian context, additional challenges may apply and should be considered to ensure that the research carried out is ethical and feasible.

Therefore, risk–benefit assessments should be conducted to ensure that potential risks are minimized and justified by expected benefits. Importantly, well-designed research following these principles can provide significant benefits for individuals and communities. Preventing exploitation, ensuring a fair selection of participants, and promoting equitable access to potential benefits of participation in the research are essential. Engaging mothers/caregivers and communities in the design of studies and interventions, as described in the previous key message, can facilitate research that is appropriate, acceptable, and responsive to their needs.

Careful consideration should be given to the balance between rigour and feasibility, with special attention paid to ethical considerations related to human rights, protection, and equity. Further guidance is provided in resources such as the WHO *Ethics in epidemics, emergencies and disasters: research, surveillance and patient care training manual (34)*, the Council for International Organizations of Medical Sciences (CIOMS) *International ethical guidelines for health-related research involving humans (35)*, and the World Medical Association (WMA) *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants (36)*.

Effectiveness evidence generation

Design and conduct high-quality randomized trials of interventions whenever appropriate

Randomized controlled trials yield the most robust evidence in terms of demonstrating causality and minimizing confounding, resulting in higher confidence that observed effects can be attributed to an intervention. Wherever ethically and operationally possible, researchers assessing interventions for infants and children with wasting and nutritional oedema are strongly advised to conduct high-quality individually randomized controlled trials or cluster-randomized controlled trials.

In addition to parallel-group randomized controlled trials, other trial designs could include crossover and factorial trials. Innovative approaches to trial design, such as adaptive platform trials, may be considered if they can answer the research question more efficiently. When sufficiently large and carefully planned, adaptive platform trials may be used to evaluate multiple interventions or combinations of interventions or to explore effects in specific subgroups to determine who may benefit most from interventions.

Researchers are encouraged to follow the WHO *Guidance for best practices in clinical trials (33)*. It is important to also consider the WHO guideline development process during trial design, aligning with the *WHO handbook for guideline development, 2nd Edition* which follows GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods *(3)*.

In line with this, it is important to take and clearly report deliberate actions to minimize the risk of bias, with particular attention given to criteria in the Cochrane risk-of-bias tool for randomized trials (RoB 2) *(37)*. This includes the domains of bias for individually randomized parallel-group trials, as set out in Box 7. Other versions of RoB 2 are available for cluster-randomized controlled trials and crossover trials *(37)*.

Situations may exist where high-quality non-randomized studies may be the only option available to understand the effects of interventions, and sometimes there are ethical reasons why randomization must not be done. Examples may be assessments of health system interventions or programme adaptations.

Non-randomized study designs could include non-randomized controlled trials such as quasi-randomized trials and observational studies of interventions such as controlled before-after studies, interrupted time series, and repeated measures studies.

If non-randomized studies are performed, they should be carefully planned, analysed, and reported to ensure rigour and transparency. Criteria in the Risk Of Bias In Non-randomized Studies – of Interventions, Version 2 (ROBINS-I V2) should be referenced to reduce risk of material bias in non-randomized studies, which may reduce risk of bias and support higher-certainty evidence *(38)*. The ROBINS-I V2 includes the seven domains outlined in Box 8.

When even non-randomized studies are not feasible in the near term, such as during emergencies, WHO's ethical framework, Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) in *Emergency use of unproven clinical interventions outside clinical trials: ethical considerations* should be followed. In such cases, where interventions are provided outside of trials, efforts should be made for evidence generation and transition to trials where possible *(39)*.

Researchers should specify study designs and methods in trial registries, protocols, reports, and publications *(38)*. Further details about protocols and methods are outlined later in this guidance.

Use diverse and inclusive selection criteria in terms of populations of infants and children

Researchers should use broad inclusion criteria that are representative of the heterogeneity of infants and children with wasting and nutritional oedema. Studies should aim to include infants and children of different ages and sexes; those with comorbidities such as HIV or tuberculosis, or disabilities which may have a relationship with nutritional status; those with varying degrees of wasting or nutritional oedema; the type of admission (new or readmission/relapse); and birth weight (for infants less than 6 months of age).

Applying diverse and inclusive selection criteria avoids unjustified and unfair exclusion criteria and ensures that evidence is applicable and directly relevant for target populations including those at higher risk of poorer outcomes. If this is not possible in all cases, consider in advance and describe how results may or may not be generalizable to subgroups not included in the study, and how subsequent research could be designed to include these populations.

Box 7. Domains of bias for individually randomized parallel-group trials in RoB 2 *(37)*

- Risk of bias arising from the randomization process
- Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
- Risk of bias due to missing outcome data
- Risk of bias in measurement of the outcome
- Risk of bias in selection of the reported result

Box 8. Domains of bias for non-randomized studies of interventions in ROBINS-I V2 *(38)*

- Risk of bias due to confounding
- Risk of bias in classification of interventions
- Risk of bias in selection of participants into the study (or into the analysis)
- Risk of bias due to deviations from intended interventions
- Risk of bias due to missing data
- Risk of bias arising from measurement of the outcome
- Risk of bias in selection of the reported result.

It is important that there is sufficient detail presented for characterization of the study population, including relevant subgroups. Depending on the type of intervention being evaluated, whether focusing on prevention or management of wasting and nutritional oedema, it may also be relevant to evaluate factors such as breastfeeding status and food availability, intake, and seasonality.

Conduct studies in diverse research settings and contexts

Ideally, research for the prevention and management of wasting and nutritional oedema should be conducted in settings where programmes and interventions are delivered in practice, not only in highly-resourced research settings. These settings should include high-risk contexts with special consideration given to research where there is a recent or ongoing humanitarian crisis. The choice of setting, however, should be guided by the research question as well as factors such as feasibility and ethical considerations.

Geographical and population-specific representation are also relevant,[11] with a need for research on interventions for wasting and nutritional oedema across WHO regions where wasting and nutritional oedema occur.

This aligns with the key message on the use of broad inclusion criteria within research around wasting and nutritional oedema, ensuring the generalizability and representativeness of research findings.

Clearly outline specifications of interventions and their delivery

Intervention and co-intervention[12] details should be clearly outlined, specifying all relevant aspects – and the logic or rationale behind them – for example, duration of intervention; who delivered the intervention; the delivery platform; and other relevant characteristics, as relevant.

When conducting cluster-randomized controlled trials,[13] all participants within specific clusters should receive the same interventions and co-interventions.

For studies evaluating prevention interventions, it is also relevant to outline the drivers of wasting that interventions are aiming to address. Studies evaluating dietary interventions should clearly outline any recipes, composition, and formulations of foods and diets.

Information about interventions and co-interventions should ideally be reported following the 12 essential items in a TIDieR (Template for Intervention Description and Replication) checklist *(41)*. Any deviations from planned interventions should be clearly reported on.

To ascertain the effects of specific co-interventions and combinations of interventions, factorial trials or adaptive platform trials may be considered, as described in an earlier key message.

If possible, intervention fidelity and other relevant pre-specified implementation outcomes should be measured and reported, which could be done qualitatively, quantitatively, or through mixed methods.

These actions will enable replicability across trials, facilitate appropriate synthesis of evidence, and inform recommendations and corresponding implementation considerations and operational guidance.

[11] Much of the research that informed the 2023 WHO guideline was conducted in settings in the WHO Africa Region, with many gaps in evidence in the South-East Asia Region, Eastern Mediterranean Region, and Western Pacific Region especially *(1)*.

[12] Co-interventions may be part of standard of care or interventions, and could include approaches such as treatment of comorbidities, giving antibiotics, cash transfers, water, sanitation and hygiene programmes, vaccination, micronutrients, maternal-directed interventions, etc.

[13] Cluster-randomized controlled trials have distinct ethical issues, including around informed consent and risk. Researchers should ensure that these issues are considered and adequately addressed, and informed by guidance such as the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials *(40)*.

Include relevant comparison arms based on current recommendations or standard of care

Where possible, comparators should reflect current WHO guidelines or standards of care to ensure that the results of trials can be used to inform recommendations. In line with international ethical guidance including the CIOMS *International ethical guidelines for health-related research involving humans* (Guideline 5) *(35)*, and the WMA *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants* (Article 33) *(36)*, participants in comparison arms should receive the best proven intervention, except in situations where no such intervention exists or where a different intervention is ethically justified.

Comparators should be justified and clearly described in protocols and publications, following the TIDieR checklist described earlier *(41)*. WHO-recommended interventions are the preferred comparator, but national or local standards of care are acceptable if there is a clear rationale (for example reflecting practice within certain contexts), with consultation with relevant local interest holders.

Details about care models should be clearly described and the level of care should not differ between study arms for ethical reasons and for determining the effects of interventions of interest.

Efforts should also be made to reduce contamination in cluster-randomized controlled trials, which is when participants in the comparison arm are inadvertently exposed to the intervention (or vice versa).

In rare cases, studies may provide no intervention if ethically sound and where there is no currently recommended intervention or treatment. Because the management of wasting and nutritional oedema always requires comprehensive assessment, care, and support, such as the treatment of medical and psychosocial problems leading to or exacerbating wasting and nutritional oedema, it would not be acceptable to provide no intervention in a comparison arm of a research study.

Importantly, historical controls, which are comparison groups of infants and children who received standard of care or an older type of intervention prior to the introduction of an intervention of interest, should generally not be used to understand the effects of interventions within studies. This is because the possibility for high risk of bias and time-related changes make it challenging to attribute differences in outcomes to interventions.

Measure and report outcomes included in core outcome sets

Core outcome sets (COSs) developed for use in effectiveness trials on wasting and nutritional oedema, outlined in the subsequent chapter of this guide, should be used for measuring and reporting outcomes *(42)*.

A COS is “an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care” (COMET Initiative) *(20)*. The COSs are intended to be used by researchers to ensure that at a minimum, data for these outcomes are reported for all effectiveness trials in infants and children with wasting and nutritional oedema.

Should a COS outcome not be included in the protocol or not reported, justification should be provided as to the reasons why – whether this is due to incomplete data, small sample size, the inability to collect some aspect of the data, an incompatible study design, resource limitation, or other.

Importantly, the COSs do not specify the primary outcome(s) for every trial, which must be given careful consideration by those designing and conducting the research. The primary outcome for a specific trial may or may not be an outcome that is included in the COS.

In addition, the COSs do not provide an exhaustive list of all outcomes that may need to be measured for every trial; the full list of outcomes may depend on the nature of the intervention being evaluated. For prevention, in particular, it is useful to consider a theory of change for how interventions may influence outcomes. Community engagement may reveal further relevant outcomes to be included in research.

Report on adverse events consistently and comprehensively

Adverse events[14] should ideally be classified by severity, including serious adverse events *(43)*. Reporting of harms, if applicable to the trial, should follow the 2025 CONSORT (CONsolidated Standards Of Reporting Trials) Statement with details about how harms are defined and assessed *(44)*.

Withdrawals and discontinuation of studies or interventions should be documented in detail. Hospitalizations and mortality should also be reported clearly, with mortality[15] being an outcome included in the COS for wasting and nutritional oedema *(42)*.

Assess outcomes at appropriate timepoints with sufficient follow-up duration

Outcome timepoints should be appropriately selected for the type of intervention and potential impact on outcomes. It is important to note that many studies in infants and children with wasting and/or nutritional oedema have measured outcomes at timepoints that align with operational endpoints, meaning that children may be included in studies for different durations. It is strongly advised that timepoints are prespecified and separated from routine management of wasting and/or nutritional oedema.

Depending on the population (including associated factors such as comorbidities), intervention, and setting, it may be important to include timepoints that capture immediate treatment responses for certain studies (for example, for outcomes such as electrolytes in trials evaluating rehydration protocols), while for other studies longer follow-up duration may be needed to evaluate outcomes like sustained recovery or neurodevelopment following an intervention.[16]

Loss to follow-up should be documented and appropriate statistical analyses completed and clearly reported on to understand the impact of missing data on findings at different timepoints. Specifically, these analyses would determine if conclusions differed between participants who were lost to follow-up and those who were retained.

Ensure that sample sizes are adequate for precise estimates around relevant outcomes

The assessments of certainty and decisions made in developing WHO recommendations are based not on statistical criteria or boundaries, but rather the precision around the estimate of the effect, with higher certainty where there is greater precision *(45–47)*.

In the context of evidence synthesis, estimates from a small body of evidence are usually less precise than those from a larger body of evidence. However, other factors may affect precision. For binary outcomes, precision can increase as the number of events increases, the total sample size increases, or when the effect size is larger. For continuous outcomes, precision can increase when sample size increases or when the variability in individual measurements decreases *(47)*.

Trials should aim to have sufficient sample sizes to obtain precise estimates with adequate power for primary outcomes and potentially core outcomes, if possible and relevant to the intervention and population. Sample sizes should be clearly justified and reported on in protocols.

It is highly advisable to conduct trials, such as multicentre trials, with sufficient clusters (for cluster-randomized controlled trials specifically) and participants to enable subgroup analyses to determine the effects of interventions in different subgroups of infants and children with or at risk of poor growth and development, wasting, and/or nutritional oedema.

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[14] Harms – often called adverse events – are defined by CONSORT as "the totality of possible adverse consequences of an intervention or therapy; they are the direct opposite of benefits, against which they must be compared" *(43)*. Examples of adverse events include severe infections or sepsis, failure to respond, electrolyte imbalance, and mortality.

[15] Although not all trials may be powered for mortality and every other outcome in the COS, data for these outcomes should still be shared regardless for the purpose of evidence synthesis.

[16] Further guidance and key points about outcome measurement and reporting is described along with the COSs *(42)*.

Provide detailed analyses for each outcome with data disaggregated by subgroup

Statistical analysis plans should be developed a priori, ideally preregistered, finalized before unblinded outcome data are available for analysis (including any subgroup and sensitivity analyses), and published alongside trial protocols. Interim analyses, if appropriate, should be preplanned. Any post hoc analyses should be identified as such.

Intention-to-treat should be the primary analysis to understand the effects of interventions within randomized trials. Intention-to-treat analysis means that all participants who were randomized are included in an analysis and are analysed according to the group to which they were originally assigned, regardless of which intervention they received.

However, the choice of analysis should align with the research question and effect of interest.[17] Per-protocol analyses, which would involve excluding participants who did not strictly follow the study protocol in terms of adhering to the intervention to which they were assigned, may also be presented if desired and appropriate. If a per-protocol analysis is justified, it should be specified in the original analysis plan.

The 2025 CONSORT Statement should be followed for conducting and reporting statistical analyses *(44)*. For each outcome, the following details should be presented by the group:

- the number of participants included in the analysis;
- the number of participants with available data at the outcome time point;
- results for each group, and the estimated effect size and its precision (such as 95% confidence interval);
- for binary outcomes, presentation of both absolute and relative effect size.

Data should be disaggregated by subgroups including age, sex, breastfeeding status, comorbidity or disability, varying degrees of wasting or nutritional oedema, birth weight (for infants less than 6 months of age), and setting.[18] This is to align with the earlier key messages about diverse and inclusive selection criteria and research across settings and contexts. PROGRESS-Plus identifiers may be used to identify characteristics of disadvantaged infants and children and mothers/caregivers[19] *(49)*. (Further details are outlined in the subsequent key message on developing and following a data management and sharing plan.)

Perform cost–effectiveness evaluations in relation to relevant outcomes

Where resources and capacity allow, cost–effectiveness analyses,[20] or cost–minimization analyses where outcomes are equivalent, should be integrated into evaluations of effectiveness of interventions, including randomized controlled trials. This requires determining appropriately the associated costs of the standard of care and interventions to undertake cost–effectiveness analysis. (Further details are outlined in the subsequent key message on data on resources.)

Cost–effectiveness analyses compare the costs of an intervention with its natural outcomes, which may be measured using indicators such as cases of wasting treated or cases averted *(50)*. Cost–effectiveness analyses should use the same intention-to-treat principle as described earlier, including all eligible participants analysed in the groups to which they were originally assigned.

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17 The International Council on Harmonization (ICH) E9(R1) Addendum provides further guidance about statistical methods for trials including the use of estimands *(48)*.

18 Studies may not always be powered to detect differences at the subgroup level, but disaggregated data should be presented where possible. Disaggregated data could be presented in supplementary material if they do not fit within the main body of publications.

19 PROGRESS-Plus refers to: place of residence; race/ethnicity/culture/language; occupation; gender/sex; religion; education; socioeconomic status; social capital; personal characteristics associated with discrimination; features of relationships; and time-dependent relationships *(49)*.

20 Cost–effectiveness analyses may report average cost–effectiveness ratios (ACERs), defined as total costs divided by total outcomes within an intervention arm. However, incremental cost–effectiveness ratios (ICERs), which compare additional costs and effects of interventions relative to alternatives, are generally preferred for informing decisions between intervention options while ACERs have been used when looking at multiple interventions for a new program such as a health benefit package.

Cost–benefit analyses compare the costs of an intervention with the outcomes measured as monetary gains associated with that intervention. In the context of wasting and nutritional oedema prevention, cost–benefit analyses may be done to compare the costs for the prevention of wasting and nutritional oedema with the potential savings in wasting treatment costs, productivity costs, and other relevant costs resulting from preventing children from becoming wasted *(50)*.

Furthermore, cost–utility analyses are similar to cost–effectiveness analyses except that they express health benefits of an intervention in a standardized measure of health, such as disability-adjusted life years (DALYs) averted, which may facilitate comparison of interventions in these populations across the health system.

Those who conduct research should consider the challenges when performing cost–effectiveness evaluations, especially in settings where there is a recent or ongoing humanitarian crisis where variability in costs, data availability, and delivery platforms may affect estimates. Given uncertainty in costs, outcomes, and assumptions, sensitivity analyses should be conducted to assess the robustness of cost and cost–effectiveness estimates under different scenarios and parameter values. Standards for reporting economic data such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Statement should be used *(51)*.

Make protocols and methods publicly available

Studies should be prospectively registered in clinical trials registries, such as the WHO International Clinical Trials Registry Platform (ICTRP) or ClinicalTrials.gov.

Protocols for randomized trials should follow the SPIRIT 2025 Statement *(52)*. For the purpose of WHO guidelines, methods of research used to inform recommendations must be made publicly available at the time of guideline publication[21] *(17)*. However, it is highly recommended that protocols and statistical analysis plans be made publicly available before commencing the research.

Develop and follow a data management and sharing plan

Sharing data in a timely and responsible manner is encouraged, while considering relevant technical, legal, and ethical issues. Data-sharing can reduce overresearching the same populations, reduce resource utilization, and maximize the value of research, including allowing for secondary analyses and pooled analyses along with other studies to answer specific questions of interest.

The World Health Organization encourages data management and data-sharing following the FAIR Data Principles: Findable, Accessible, Interoperable, and Reusable *(53, 54)*. Acceptable options for sharing data that have been adequately anonymized by removing direct and indirect identifiers to minimize the risk of re-identification, could include using fully open repositories, or repositories that require managed access. Clear and structured metadata, which are the properties of the dataset, should always be included along with any datasets.[22]

Further information about data-sharing can be found in the WHO document *Sharing and reuse of health-related data for research purposes: WHO policy and implementation guidance (53)*.

At the time of guideline publication, both the methods of studies and the results of research used to inform the WHO recommendations must be made publicly available *(17)*.

[21] Publicly available means "the data or studies are available in print or online to the public, whether free or for a fee, irrespective of whether they are indexed in a bibliographic database" *(17)*.

[22] If these data were cleaned, the protocol or methods used should ideally be shared.

Contextual evidence generation

Aim to understand the values placed on key outcomes and their relative importance

Understanding the values,[23] or relative importance, placed on outcomes from the perspective of mothers/caregivers in relation to an intervention, is fundamental to decision-making for recommendations. This overlaps with the earlier key message about fostering inclusion, participation, and collaborative partnerships.

Qualitative methods should be adopted that include, but are not limited to, in-depth interviews, focus group discussions and observations; and/or quantitative methods, such as the use of health utility ratings.[24] These can be used to gauge the relative importance that interest holders, such as mothers/caregivers of infants and children with wasting and nutritional oedema, assign to outcomes, as well as any variability in how mothers/caregivers value the outcomes.

Significant variability or uncertainty in terms of values placed on outcomes can potentially result in conditional recommendations, rather than strong recommendations, for an intervention.

This is particularly relevant from an equity perspective, as disadvantaged populations may give precedence to different outcomes, which must be considered in the context of decision-making around interventions.

Assess the impact of interventions on health equity

Assessing the impact of interventions on health equity is essential and may influence whether recommendations are strong or conditional. Examples of specific questions to be addressed include whether:

- infants and children and their mothers/caregivers may be disadvantaged in terms of intervention options being considered;[25]
- there are differences in the relative effectiveness – or even undesirable effects and harms – of interventions in relation to being disadvantaged;[26]
- the interventions and how they are implemented ensure that inequities are not increased and, if possible, are reduced.

The effect of interventions on disadvantaged infants and children and mothers/caregivers may be evaluated quantitatively, with broad inclusion criteria that include those at higher risk of poorer outcomes, and through preplanned subgroup analysis within effectiveness trials, as described in earlier key messages. PROGRESS-Plus may be used as a framework to identify and understand disadvantaged infants and children and their mothers/caregivers *(49)*.

Qualitative data should be collected and analysed through in-depth interviews, focus group discussions, targeted observations, and/or other reliable qualitative approaches that include mothers/caregivers of infants and children with wasting and oedema, and other interest holders. Meaningful community engagement should also be undertaken to resolve any challenges that may impact equity.

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[23] The word "values" is used in this context to align with the GRADE Evidence-to-Decision framework in terms of how much people value the main outcomes *(4, 15)*.

[24] Health utility ratings indicate how important a particular health outcome is. They can be established using quantitative methods, including direct methods or indirect methods. Health utility values can also be important for cost-utility analyses, such as quality-adjusted life years (QALYs).

[25] One possible example could be low-osmolarity Oral Rehydration Solution (ORS) versus Rehydration Solution for Malnourished children (ReSoMal) for infants and children with severe wasting and/or nutritional oedema who are dehydrated but not in shock. Compared to ReSoMal, ORS is less expensive and more widely available, and can be administered at home as appropriate, which may in turn increase equity. However, the effectiveness of such interventions is central to ensure that the standard of care is sufficiently high.

[26] Interventions may be less effective in disadvantaged populations if adherence is lower due to contextual constraints, such as limited access to care or food insecurity. Additionally, children may respond differently to interventions based on their baseline risk of poor outcomes.

The Consolidated criteria for reporting qualitative research (COREQ) checklist should be followed for reporting qualitative research including interviews and focus group discussions *(55)*. The Critical Appraisal Skills Programme (CASP) Qualitative Studies Checklist can also be used to ensure that methodological limitations of qualitative research are minimized *(56)*.

Evaluate the acceptability of interventions from multiple perspectives

Acceptability, in terms of whether relevant interest holders perceive an intervention as being acceptable, should be evaluated. This may be done qualitatively from the perspectives of, for example, mothers/caregivers of infants and children with, or at risk of, wasting and nutritional oedema, other members of the household, communities, health workers, programme implementers, and policy-makers. Quantitative assessments of uptake and adherence may also be relevant to the acceptability of interventions and may require understanding additional contextual information relating to, for example, customs and beliefs around food.

As above, the COREQ checklist should be followed for reporting qualitative research including interviews and focus group discussions *(55)*. The CASP Qualitative Studies Checklist may be used to minimize methodological limitations *(56)*.

There is value in documenting and sharing information about the acceptability of interventions or delivery models from the perspective of those implementing them in practice, as well as whether acceptability of interventions affects delivery. This information can be used alongside research evidence to inform decision-making related to acceptability for the purpose of developing WHO recommendations and can also support implementation.

Tools such as the Assessing unConventional Evidence (ACE) tool may be used to ensure that sufficient detail is shared about acceptability during the implementation of interventions to be able to assess strengths and limitations of the evidence *(57)*.

Determine the feasibility, potential for scale-up, and coverage of interventions

Quantitative methods can aid in understanding the feasibility and potential for scaling up[27] interventions within a certain geographical area. This should be from the perspectives of the health system and providers of interventions, as well as of mothers/caregivers and other interest holders, depending on the nature of the intervention.

For qualitative research, including interviews and focus group discussions, the COREQ checklist should be used *(55)*. The CASP Qualitative Studies Checklist can also be referred to for reducing methodological limitations *(56)*.

Other key factors affecting the implementation of interventions include possible resource allocation; health system capacity; local food system and supply chains; and necessary personnel requirements and training. Operational research, described later in this guidance, may be carried out to further understand these factors, along with implementation and coverage. Consideration should also be given to context-specific delivery models and adaptation of interventions across different settings including humanitarian contexts. Furthermore, in settings where interventions are integrated into primary healthcare systems, those conducting research should consider evaluating service delivery models, task-sharing, health worker capacity, and resource-use including cost comparisons.

[27] Scaling up can be defined as "deliberate efforts to increase the impact of health service innovations successfully tested in pilot or experimental projects so as to benefit more people and to foster policy and programme development on a lasting basis" *(58)*.

As above, it is relevant to document and share information about the feasibility of implementing interventions as well as the factors that affect feasibility, from the perspective of implementers. The ACE (Assessing unConventional Evidence) tool may be used to ensure that there is sufficient detail for evaluating strengths and limitations of the evidence *(57)*.

Obtain and present data on resource use from different costing perspectives

It is relevant to understand resource-use for the purpose of developing recommendations, as resource implications are a determining factor in the direction and strength of recommendations *(3)*. Moreover, costs incurred by beneficiaries including mothers/caregivers or households (opportunity costs) may have negative impacts on equity.

The total costs or resource-use associated with implementing interventions for infants and children with wasting and nutritional oedema should be estimated.

To understand the feasibility and potential scalability of costs, those incurred from different perspectives should be presented, including costs to mothers/caregivers and families,[28] such as expenses, time spent seeking care, lost wages due to not working, and costs to providers and the health system *(50)*. Cost–efficiency, expressed as the cost per relevant programme input or output (for example, cost per child treated), should also be calculated.

Cost data should be disaggregated as much as possible to support transparency and facilitate modelling. Financial and economic costs, as well as direct and indirect costs,[29] should be clearly reported with clarity as to what is included in costs and budgets and what is excluded.

As outlined in the key message on cost–effectiveness analyses, sensitivity analyses should be conducted to characterize the variability and uncertainty in key cost and outcome parameters, such as unit costs, resource use, programme coverage, and intervention effectiveness.

Share detailed information about how interventions are implemented within programmes

Understanding the details of intervention implementation within programmes and context – beyond what is described above – is useful when answering specific questions about acceptability, feasibility, and resource-use. This can give insight into whether or not an intervention works in practice, as well as what challenges may be encountered and how they can be addressed. It is also helpful to understand how to replicate interventions and assess the potential for their scale-up in different contexts.

The WHO *Programme reporting standards for sexual, reproductive, maternal, newborn, child and adolescent health* may be used to report systematically on implementation, including programme overview; programme components and implementation; the monitoring of implementation; evaluation and results; and synthesis *(59)*. It is important to also provide clarity as to who delivers programmes and services, such as governments, nongovernmental organizations, etc., and to consider potential influences related to power imbalances, governance, and accountability mechanisms within health systems. The health systems perspective may be especially important in settings with a recent or ongoing humanitarian crisis where health system capacity and resilience are affected.

Impact evaluations may also be conducted to determine what is effective in terms of implementation of interventions within programmes. Randomized controlled trials are optimal designs for impact evaluation, yet other designs may be considered, such as quasi-experimental impact evaluations. Further guidance can be found in existing tools such as *Evaluating the impact of interventions addressing health behaviour: considerations and tools for policy-makers (60)*. Principles in the section on effectiveness evidence generation within this guidance should also be considered for impact evaluations.

[28] This is often referred to as "beneficiary costs".

[29] Examples of direct costs would be medicines, therapeutic foods, transportation costs for caregivers, etc; examples of indirect costs would be opportunity costs of caregiver time, reduced household income, etc.

Document any unintended positive and negative consequences resulting from implementing an intervention

Those who implement interventions within programmes or studies should report any unintended positive and negative consequences of the implementation, in addition to any prespecified outcomes. Ideally, there should be a prespecified monitoring plan to identify and document potential unintended consequences, using qualitative and/or quantitative methods as appropriate. These consequences may influence the balance of desirable and undesirable effects of interventions as well as other domains such as equity, acceptability, and feasibility.

Possible unintended positive consequences may include greater coverage, increased adherence to interventions, strengthened monitoring systems, and earlier care-seeking behaviours. Important examples of unintended negative consequences may be around antimicrobial resistance, displacement of breast milk or interference with breastfeeding, hospital-acquired infections, or other indirect harms at household or health-system level.

3.C Core outcome sets for effectiveness trials on wasting and nutritional oedema

Within the Delphi process to develop COSs, 25 of 36 invited participants completed the round 1 survey between June and July 2024, and 25 of 36 completed the round 2 survey between July and August 2024. Participants were based in 21 countries, including 14 low- and middle-income countries. For the eight consensus meetings that took place between October and November 2024 there were 24 participants from 17 countries including 13 low- and middle-income countries, with an average of 13 participants per meeting.

The consolidated guidance and key points about outcome definitions, measurement and reporting raised by the expert panel during the consensus meetings were tabulated. The expert panel had continuous discussions during the consensus meetings about how prescriptive or rigid the definitions, measurement and reporting should be and agreed that a flexible approach was appropriate in some areas, with the rationale clearly documented. The outcomes for each of these respective COSs are presented in Tables 7 to 12, along with guidance and key points on outcome measurement and reporting. Table 13 includes the COSs for the prevention of wasting and nutritional oedema with guidance and also provides key points on outcome measurement and reporting. Additional discussion points from the consensus meetings on outcome measurement and reporting are presented narratively by outcome domain. Further information can be found in an original paper published in BMJ Global Health *(42)*.

Table 7. Overview of core outcome sets for effectiveness trials focused on management of infants and children with wasting and nutritional oedema

Infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – inpatient settings	Infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – outpatient/community settings	Infants and children 6–59 months of age with severe wasting and/or nutritional oedema – inpatient settings	Infants and children 6–59 months of age with severe wasting or nutritional oedema – outpatient/community settings	Infants and children 6–59 months of age with moderate wasting – outpatient/community settings
Mortality	Mortality	Mortality	Mortality	Mortality
Weight change (g/kg/day)	Weight change (g/kg/day)	–	Weight change (g/kg/day)	Weight change (g/kg/day)
–	Mid-upper arm circumference (MUAC)	–	Mid-upper arm circumference (MUAC)	Mid-upper arm circumference (MUAC)
–	Weight-for-age z-scores (WAZ)	–	Weight-for-age z-scores (WAZ)	Weight-for-age z-scores (WAZ)
Oedema resolving	–	Oedema resolving	Oedema resolving	–
Clinical improvement	–	Clinical improvement	–	–
Clinical deterioration	–	Clinical deterioration	–	–
Recovery from morbidity	Morbidity or recovery from morbidity	Recovery from morbidity	–	–
Breastfeeding indicators	Breastfeeding indicators	–	–	–
–	Anthropometric recovery[a]	–	Anthropometric recovery	Anthropometric recovery
–	–	–	Time to anthropometric recovery	–
–	Non-response[a]	–	Non-response	Non-response
–	–	–	–	Deterioration to severe wasting and/or nutritional oedema
Sustained recovery	Sustained recovery[a]	Sustained recovery	Sustained recovery	Sustained recovery

[a] Applies to infants with wasting and/or nutritional oedema, rather than infants with underweight only

Table 8. Core outcome set for infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – interventions in inpatient settings

Outcomes	Guidance and key points about outcome measurement and reporting[a]
Mortality	All-cause mortality, to be reported as a binary outcome
Weight change (g/kg/day)	Rate of weight change in grams per kilogram body weight per day (g/kg/day), to be reported as a continuous outcome While weight change is considered a critical outcome for this population, the optimal rate of weight gain has not yet been established
Oedema resolving	Bilateral oedema grade improved or resolution of bilateral oedema, to be reported as a binary outcome
Clinical improvement	Based on clinical and nutritional signs, to be reported as a binary outcome
Clinical deterioration	Based on clinical signs or need for clinical interventions/support, to be reported as a binary outcome Reporting of clinical deterioration is an ethical requirement for trials, and is also seen as a critical outcome
Recovery from morbidity	Resolution of medical problems that prompted admission for inpatient care, to be reported as a binary outcome
Breastfeeding indicators	For example, exclusive breastfeeding in infants less than 6 months of age, to be reported as a binary outcome
Sustained recovery	Anthropometric recovery sustained ideally for at least 6 months, to be reported as a binary outcome This outcome should be reported in any trial with post-exit anthropometric outcomes for as long as infants were followed up after exit If the follow-up time is shorter or data cannot be reported, researchers should include a statement in the limitations section Reporting on sustained recovery also accounts for relapse and readmission, which were not individually deemed critical outcomes

[a] Guidance and key points about outcome measurement and reporting emerged from discussion with participants during the consensus meetings

Table 9. Core outcome set for infants less than 6 months of age with wasting and/or nutritional oedema and/or underweight – interventions in outpatient/community settings

Outcomes	Guidance and key points about outcome measurement and reporting[a]
Mortality	All-cause mortality, to be reported as a binary outcome
Weight change (g/kg/day)	Rate of weight change in grams per kilogram body weight per day (g/kg/day), to be reported as a continuous outcome While weight change is considered a critical outcome for this population, the optimal rate of weight gain has not yet been established
Mid-upper arm circumference (MUAC)	Mid-upper arm circumference (MUAC) in mm, to be reported as a continuous outcome
Weight-for-age z-scores (WAZ)	Weight-for-age z-scores (WAZ) based on the 2006 WHO child growth standards, to be reported as a continuous outcome
Morbidity or recovery from morbidity	Episodes of morbidity or resolution of medical problems, to be reported as a continuous outcome if capturing the number of episodes or as a binary outcome for resolution of medical problems
Breastfeeding indicators	For example, exclusive breastfeeding in infants less than 6 months of age, to be reported as a binary outcome
Anthropometric recovery[b]	Recovery based on anthropometric indicators, to be reported as a binary outcome
Non-response[b]	Not achieving anthropometric recovery within 4 months of initiating treatment, to be reported as a binary outcome
Sustained recovery[b]	Anthropometric recovery sustained ideally for at least 6 months, to be reported as a binary outcome This outcome should be reported in any trial with post-exit anthropometric outcomes for as long as infants were followed up after exit; the duration of follow-up may be dependent on the type of intervention (e.g. dietary or non-dietary) If the follow-up time is shorter or data cannot be reported, researchers should include a statement in the limitations section Reporting on sustained recovery also accounts for relapse and readmission, which were not individually deemed critical outcomes

[a] Guidance and key points about outcome measurement and reporting emerged from discussion with participants during the consensus meetings

[b] Applies to infants with wasting and/or nutritional oedema, rather than infants with underweight only

Table 10. Core outcome set for infants and children 6–59 months of age with severe wasting and/or nutritional oedema – interventions in inpatient settings

Outcomes	Guidance and key points about outcome measurement and reporting[a]
Mortality	All-cause mortality, to be reported as a binary outcome
Oedema resolving	Bilateral oedema grade improved or resolution of bilateral oedema, to be reported as a binary outcome
Clinical improvement	Based on clinical and nutritional signs, to be reported as a binary outcome
Clinical deterioration	Based on clinical signs or need for clinical interventions/support, to be reported as a binary outcome Reporting of clinical deterioration is an ethical requirement for trials, and is also seen as a critical outcome
Recovery from morbidity	Resolution of medical problems that prompted admission for inpatient care, to be reported as a binary outcome
Sustained recovery	Anthropometric recovery sustained ideally for at least 6 months, to be reported as a binary outcome This outcome should be reported in any trial with post-exit anthropometric outcomes for as long as infants and children were followed up after exit If the follow-up time is shorter or data cannot be reported, researchers should include a statement in the limitations section Reporting on sustained recovery also accounts for relapse and readmission, which were not individually deemed critical outcomes

[a] Guidance and key points about outcome measurement and reporting emerged from discussion with participants during the consensus meetings

Table 11. Core outcome set for infants and children 6–59 months of age with severe wasting or nutritional oedema – interventions in outpatient/community settings

Outcomes	Guidance and key points about outcome measurement and reporting[a]
Mortality	All-cause mortality, to be reported as a binary outcome
Weight change (g/kg/day)	Rate of weight change in grams per kilogram body weight per day (g/kg/day), to be reported as a continuous outcome While weight change is considered a critical outcome for this population, the optimal rate of weight gain has not yet been established
Mid-upper arm circumference (MUAC)	Mid-upper arm circumference (MUAC) in mm, to be reported as a continuous outcome
Weight-for-age z-scores (WAZ)	Weight-for-age z-scores (WAZ) based on the 2006 WHO child growth standards, to be reported as a continuous outcome
Oedema resolving	Bilateral oedema grade improved or resolution of bilateral oedema, to be reported as a binary outcome
Anthropometric recovery	Recovery based on anthropometric indicators, to be reported as a binary outcome
Time to anthropometric recovery	Days until anthropometric recovery has been achieved, to be reported as a continuous outcome
Non-response	Not achieving anthropometric recovery within 4 months of initiating treatment, to be reported as a binary outcome
Sustained recovery	Anthropometric recovery sustained ideally for at least 6 months, to be reported as a binary outcome This outcome should be reported in any trial with post-exit anthropometric outcomes for as long as infants and children were followed up after exit; the duration of follow-up may be dependent on the type of intervention (e.g. dietary or non-dietary) If the follow-up time is shorter or data cannot be reported, researchers should include a statement in the limitations section Reporting on sustained recovery also accounts for relapse and readmission, which were not individually deemed critical outcomes

[a] Guidance and key points about outcome measurement and reporting emerged from discussion with participants during the consensus meetings

Table 12. Core outcome set for infants and children 6–59 months of age with moderate wasting – interventions in outpatient/community settings

Outcomes	Guidance and key points about outcome measurement and reporting[a]
Mortality	All-cause mortality, to be reported as a binary outcome
Weight change (g/kg/day)	Rate of weight change in grams per kilogram body weight per day (g/kg/day), to be reported as a continuous outcome While weight change is considered a critical outcome for this population, the optimal rate of weight gain has not yet been established
Mid-upper arm circumference (MUAC)	Mid-upper arm circumference (MUAC) in mm, to be reported as a continuous outcome
Weight-for-age z-scores (WAZ)	Weight-for-age z-scores (WAZ) based on the 2006 WHO child growth standards, to be reported as a continuous outcome
Anthropometric recovery	Recovery based on anthropometric indicators, to be reported as a binary outcome
Non-response	Not achieving anthropometric recovery within 4 months of initiating treatment, to be reported as a binary outcome
Deterioration to severe wasting and/or nutritional oedema	Progression to severe wasting and/or nutritional oedema based on anthropometric indicators and/or bilateral oedema, to be reported as a binary outcome
Sustained recovery	Anthropometric recovery sustained ideally for at least 6 months, to be reported as a binary outcome This outcome should be reported in any trial with post-exit anthropometric outcomes for as long as infants and children were followed up after exit; the duration of follow-up may be dependent on the type of intervention (e.g. dietary or non-dietary) If the follow-up time is shorter or data cannot be reported, researchers should include a statement in the limitations section Reporting on sustained recovery also accounts for relapse and readmission, which were not individually deemed critical outcomes

[a] Guidance and key points about outcome measurement and reporting emerged from discussion with participants during the consensus meetings

Table 13. Core outcome set for prevention of wasting and nutritional oedema

Outcomes	Guidance and key points about outcome measurement and reporting[a]
Prevalence of wasting and/or nutritional oedema	The proportion of children with wasting (based on mid-upper arm circumference [MUAC] and/or weight-for-height z-scores [WHZ]) and/or nutritional oedema at a specific follow-up time, to be reported as a binary outcome To be included in population- or community-based trials The impact of seasonality must be assessed and should be accounted for if relevant, with prevalence being measured at baseline and follow-up at the same time of year
Prevalence of severe wasting and/or nutritional oedema	The proportion of children with severe wasting (based on mid-upper arm circumference [MUAC] and/or weight-for-height z-scores [WHZ]) and/or nutritional oedema at a specific follow-up time, to be reported as a binary outcome To be included in population- or community-based trials The impact of seasonality must be assessed and should be accounted for if relevant, with prevalence being measured at baseline and follow-up at the same time of year
Incidence of wasting and/or nutritional oedema	The number of new cases of wasting (based on mid-upper arm circumference [MUAC] and/or weight-for-height z-scores [WHZ]) and/or nutritional oedema over a specific time interval, to be reported as a rate To be included in individually randomized trials, as well as in population- or community-based trials whenever possible
Incidence of severe wasting and/or nutritional oedema	The number of new cases of severe wasting (based on mid-upper arm circumference [MUAC] and/or weight-for-height z-scores [WHZ]) and/or nutritional oedema over a specific time interval, to be reported as a rate To be included in individually randomized trials, as well as in population- or community-based trials whenever possible
Mid-upper arm circumference (MUAC)	Mid-upper arm circumference (MUAC) in mm, to be reported as a continuous outcome
Weight-for-length z-scores (WLZ) or weight-for-height z-scores (WHZ)	Weight-for-length z-scores (WLZ) or weight-for-height z-scores (WHZ) based on the 2006 WHO child growth standards, to be reported as a continuous outcome
Morbidity	Presence of morbidity which may be based on inpatient admissions and/or outpatient clinic visits, to be reported as a binary outcome or continuous outcome if capturing multiple visits per child Morbidity data may be of poor quality, and therefore effort should be made to reduce risk of bias around reporting and measurement of this outcome

[a] Guidance and key points about outcome measurement and reporting emerged from discussion with participants during the consensus meetings

Through this COS development process, the expert panel decided that it would not be appropriate to define all outcomes or be too prescriptive in the COSs given that measurement approaches and clinical practice may evolve over time. Several outcomes in the COSs rely on clinical judgement or subjective assessment, such as through clinical examination or for certain breastfeeding indicators like effective breastfeeding. The expert panel also highlighted that an aim of the COS would be to agree on the critical outcomes and to guide researchers in how to optimally report data, but not how to interpret data. Further consideration is needed regarding outcomes for research studies versus indicators for programmes on wasting and nutritional oedema, which was beyond the scope of this COS development exercise.

The expert panel also identified several outcomes requiring further conceptual and methodological work beyond what was feasible within this COS development process. The expert panel acknowledged that further exploration is needed to better understand outcomes and how they relate to each other, potentially supported by the development of a conceptual framework of surrogate and target outcomes. Specific outcomes require more research, such as the optimal rate of weight gain, which remains unknown. Non-response is another outcome that requires more consideration and conceptualisation, as well as an understanding of reasons for non-response, such as illness and/or disability in order to help address this problem in practice. The expert panel also noted that additional indicators and outcomes along the impact pathway should be examined particularly for prevention trials, to consider how interventions may impact incidence or prevalence of wasting and nutritional oedema as endpoints.

4. Updating WHO guidance

The World Health Organization aims to undertake surveillance of new evidence and will consult with the TAG every 12 months about the possible need for updating guidance. Updating may be required if there is new, potentially relevant evidence that may result in significant consequences; or if there are additional subject areas that have not yet been considered; or if the structure or scope of the guidance should be revised[30] *(61)*. Proposed triggers[31] for updating existing recommendations in the 2023 WHO guideline are included in Box 9.

Box 9. Proposed triggers for updating recommendations in the 2023 WHO guideline

- Certainty-of-evidence – when there is a change in the certainty of evidence or direction of effect that may merit a change in a given recommendation *(62)*
- Decision thresholds[32] – when a given effect size is reached *(62)*
- Contextual triggers – resources, impact on health equity, accessibility, and/or feasibility information, shifts, or changes that affect applicability or implementation.

Application of the research priority agenda to WHO guidance

Systematic reviews are used to inform WHO recommendations, with the certainty of the evidence based on the GRADE approach, which then impacts the overall certainty of recommendations *(3, 63, 64)*. Reasons that can result in downgrading the evidence according to GRADE include risk of bias; unexplained inconsistency (for example, if subgroups are not well understood); indirectness, if studies are not directly applicable or aligned to the question at hand; imprecision, which may be an issue if there are too few participants within or across studies; and publication bias *(63, 64)*.

Other criteria in the GRADE Evidence-to-Decision framework are also crucial in informing recommendations, including resource-use and cost–effectiveness, acceptability and feasibility of interventions, and potential impacts on health equity *(63)*. Several research questions, prioritized through this CHNRI exercise, aim at further understanding these GRADE domains which could directly influence the direction, strength, and certainty of WHO recommendations *(3, 63)*.

Overall, the global research priority agenda has the potential to harmonize research in key areas, which in turn could increase the certainty of the evidence that underpins recommendations.

It is important to note that there can be a distinction between research questions and guideline questions, although there is often alignment. In the CHNRI exercise to develop a research priority agenda, criteria that participants used to prioritize research questions were answerability, effectiveness, deliverability, and effect on equity *(21, 22)*. The Guideline Development Group for the 2023 WHO guideline prioritized guideline questions according to three criteria: uncertainty or controversy about best practice, availability or absence of guidance, and impact on health outcomes *(1, 65)*.

Answering research questions in this research priority agenda does not guarantee that findings will be used directly for guidance. However, the likelihood of informing recommendations increases when new, high-quality evidence meaningfully strengthens the body of evidence for a relevant guideline question and/or demonstrates impact on relevant outcomes with sufficient certainty across available studies.

[30] Additional details are included in *Chapter 9. Keeping WHO normative guidance up to date* in the *WHO handbook for the development of normative products. Volume III. Processes and procedures (61)*.

[31] These triggers, proposed by WHO and discussed by the TAG, have been adapted based on methods for trigger-based incorporation within living guideline recommendations by Akl et al *(62)*.

[32] A process to determine decision thresholds was underway at the time of publication of this research guide.

In addition to this research priority agenda, COSs should be applied for effectiveness trials in these populations to further standardize research *(42)*. Researchers should also follow the guidance on evidence generation and other WHO guidance on best practices to ensure that they are conducting ethical and high-quality research in these areas *(33)*.

5. Implementation plan

The World Health Organization and UNICEF will promote the uptake and use of this guide for research by individuals and institutions as well as by funders, ethics review committees, and institutional review boards involved in or supporting research in infants and children with or at risk of wasting and nutritional oedema. The guide represents an important coordination and capacity-strengthening initiative aimed at generating relevant, high-quality evidence around the prevention and management of wasting and nutritional oedema in infants and children.

Dissemination of this guide for research, along with a shorter summary document containing the main content, will be undertaken in collaboration with other United Nations agencies partnering on the Global Action Plan on Child Wasting *(2)*. To support awareness, activities will include sharing on WHO and UNICEF web pages, as well as meetings and webinars. WHO and UNICEF will also distribute the guide to researchers and funders directly along with the TAG and the Guideline Development Group of the 2023 WHO guideline. WHO will work closely with WHO regional and country offices to support engagement with ministries of health and other relevant national bodies.

The World Health Organization and UNICEF advise researchers and funders to explicitly reference this document in proposals for research funding, study protocols, and publications. Both WHO and UNICEF strongly encourage its use and application at various stages of research, including proposal writing, protocol development, ethical review processes, research, and analysis and publication of findings.

6. Monitoring and evaluation plan

Various monitoring and evaluation plan indicators can be used for the research priority agenda, the guidance on evidence generation, and the COSs. The indicators, outlined in Box 10, are intended to monitor uptake, alignment, and influence of this guide, which may be updated, and to aid with surveillance of new evidence. The indicators will be assessed based on clinical trial registries, published literature including primary studies and systematic reviews, reports from funders and implementing agencies, and internal tracking of emerging evidence.

Box 10. Monitoring and evaluation plan indicators

Awareness indicators:

- downloads of this document and/or related publications.

Funding shape and coordination indicators:

- reference to this document and/or related publications in funding calls
- alignment with research questions in the research priority agenda and funded research
- meetings held with a focus on the research questions in the research priority agenda.

Research indicators:

- registered studies and/or published research that reference or align with research questions in the research priority agenda
- registered studies and/or published research that reference or align with key messages in the guidance on evidence generation
- registered studies and/or published research that reference and report outcomes in the COS.

7. Limitations

7.A A global research priority agenda for wasting and nutritional oedema

The World Health Organization acknowledges several limitations of the CHNRI exercise for the development of the research priority agenda, the first being the use of English in the surveys. This was an expedited process which took into account the need to rapidly produce a research priority agenda while nutrition funding has been reduced drastically *(66)*. This may have affected the research questions that were prioritized, and WHO and UNICEF urge policy-makers, researchers, research institutions, and funders to consider what research should be conducted to address needs in their settings.

The World Health Organization also acknowledges the relatively small sample size for the CHNRI exercise; however, multiple actions were taken by WHO to support and promote responses. Surveys were circulated to a broad group which included members of the Guideline Development Group, observers, and systematic review team leads for the 2023 WHO guideline; the TAG; attendees of a 2024 research consultation on wasting and nutritional oedema; and WHO regional offices and their networks including the Wasting Global Thematic Working Group of the Global Nutrition Cluster.

The CHNRI method is a metrics-based approach using surveys which has some inherent limitations. The process can be intensive for participants who must score a considerable number of research questions, including within the individual populations and topics, which can make obtaining responses more challenging, as described above. In addition, completing the surveys required a reliable Internet connection, which realistically can be a further barrier to equitable participation. These challenges may have led to a low response rate and self-selection bias *(67)*, the effects of which would be unknown in terms of impact on the prioritized research questions.

Another major limitation is that patients or caregivers/mothers of infants and children with wasting and/or nutritional oedema were not included in this CHNRI process. Conducting further participatory research would be valuable to ensure that the research questions being addressed reflect the needs of communities and individuals affected by wasting and nutritional oedema. As stated earlier, WHO and UNICEF urge policy-makers, researchers, and others to strongly consider what from this agenda is most relevant in their contexts.

7.B Guidance on evidence generation for interventions addressing wasting and nutritional oedema

A limitation of this guidance on evidence generation is that it has not been evaluated across diverse research settings; this is the first guidance of its kind for interventions addressing wasting and nutritional oedema. It therefore may be revised in light of its use and applicability. Evolving methodological standards for evidence generation may also mean that future updates are needed to ensure continued alignment with best practices.

Furthermore, the guidance emphasizes methodological rigour, which also may present challenges in terms of applying the recommended approaches in certain contexts or situations. This may be relevant in humanitarian contexts and in situations where there are, for example, funding, infrastructure, and personnel constraints.

7.C Core outcome sets for effectiveness trials on wasting and nutritional oedema

With regard to the COS development process, a limitation is that patients and caregivers were not included. There are concerns around the sensitivity of discussing outcomes such as mortality in infants and children, which would make it challenging to include their caregivers or families. WHO also acknowledges that the two surveys and consensus meetings were all conducted virtually, which could have presented challenges in identifying and involving caregivers of infants and children with wasting and nutritional oedema across settings and contexts.

Involving caregivers would be an important next step in the evolution of these COSs to ensure that outcomes are considered truly important by patients, caregivers, and communities based on their lived experiences.

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Annex 1. List of contributors

WHO Steering Committee

- Marina Adrianopoli, Technical Officer Nutrition, Department of Nutrition and Food Safety, Food and Nutrition Action in Health Systems Unit, WHO headquarters
- Jaden Bendabenda, Technical Officer, Department of Nutrition and Food Safety, Food and Nutrition Action in Health Systems Unit, WHO headquarters
- Allison Daniel, consultant, Department of Nutrition and Food Safety, Food and Nutrition Action in Health Systems Unit, WHO headquarters
- Laurence Grummer-Strawn, Technical Officer, Department of Nutrition and Food Safety, Food and Nutrition Action in Health Systems Unit, WHO headquarters
- Zita Weise Prinzo, Technical Officer, Department of Nutrition and Food Safety, Food and Nutrition Action in Health Systems Unit, WHO headquarters.

UNICEF Secretariat

- Kirrily de Polnay, Nutrition Specialist, UNICEF
- Grace Funnell, Nutrition Specialist, UNICEF
- Minh Tram Le, Nutrition Specialist, UNICEF

Guideline methodologists

- Celeste Naude, Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University, Stellenbosch, South Africa
- Michael McCaul, Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University, Stellenbosch, South Africa

WHO Regional Advisors

- Abdul Baseer Qureshi, WHO Eastern Mediterranean Region
- Fabio Da Silva Gomes, WHO Region of the Americas
- Padmini Angela De Silva, WHO South-East Asia Region
- Leendert Nederveen, WHO Region of the Americas
- Laetitia Ouedraogo Nikiema, WHO African Region
- Florence Turyashemererwa, WHO African Region
- Kremlin Wickramasinghe, WHO European Region

UNICEF/WHO Technical Advisory Group on Wasting and Nutritional Oedema (Acute Malnutrition)

- Aida Alsaddeeq, Al-Sadaka General Teaching Hospital, Yemen
- Caroline Antoine, Action Contre la Faim, France
- Ali Mohamed Elhag Arabi, University of Khartoum, Sudan
- James Berkley, KEMRI, Kenya/University of Oxford, United Kingdom of Great Britain and Northern Ireland
- Bindi Borg, Independent, Australia
- Colleen Emary, Global Nutrition Cluster, Canada
- Patrizia Fracassi, Food and Agriculture Organisation of the United Nations, Italy
- Kate Golden, Concern Worldwide, Ireland
- Geraldine Honton, World Food Programme, Italy
- John Kabongo, National Nutrition Programme (PRONANUT), Democratic Republic of the Congo
- Rozina Khalid, Independent, Pakistan
- Praveen Kumar, Lady Hardinge Medical College, India
- Natasha Lelijveld (TAG co-chair), Emergency Nutrition Network, Malawi
- Nicolette Nabukeera Barungi, Makerere University College of Health Sciences, Uganda
- Terry Njeri Theuri, United Nations High Commissioner for Refugees (UNHCR), Switzerland
- Temidayo Odebunmi, Federal Ministry of Health, Nigeria
- Sanne Sigh, GIZ Cambodia (German international cooperation), Cambodia
- Indi Trehan (TAG co-chair), University of Washington, United States of America

External reviewers

- Bernardette Cichon, International Rescue Committee, United Kingdom of Great Britain and Northern Ireland
- Samou Diarra, Hôpital Fousseyni DAOU de Kayes, Mali
- Fekri Dureab, University of Doha for Science and Technology, Qatar
- Anna Heath, Hospital for Sick Children, Canada
- Suvi Kangas, International Rescue Committee, Belgium
- Pearl Mallawaarachchi, Lady Ridgeway Hospital for Children, Sri Lanka
- Shuby Puthussery, University of Bedfordshire, United Kingdom of Great Britain and Northern Ireland
- Ritu Rana, World Food Programme, Italy
- Debbie Thompson, University of the West Indies, Jamaica
- Kirk Tickell, University of Washington, United States of America

WHO Ethics Review Committee

- Lee-Anne Pascoe, consultant, Health Ethics and Governance Unit, WHO
- G. Owen Schaefer, National University of Singapore, Singapore
- Ehsan Shamsi-Gooshki, Monash University, Australia
- Vicki Xafis, Independent, Australia

Donors

- Children's Investment Fund Foundation (CIFF)
- Eleanor Crook Foundation (ECF)
- European Civil Protection and Humanitarian Aid Operations (ECHO)
- Foreign, Commonwealth & Development Office of the United Kingdom of Great Britain and Northern Ireland (FCDO)
- United Nations Children's Fund (UNICEF)

Annex 2. Scores for all research questions

Research question	RPS	AEA	Population
What is the effectiveness of different ready-to-use therapeutic food (RUTF) protocol options with reducing quantities compared to standard quantities?	93.9	89.3	Severe
What are potential risk-targeted follow-up strategies of infants and children with severe wasting and/or nutritional oedema?	93.6	89.5	Severe
What are reliable criteria for defining optimal growth in infants less than 6 months of age at risk of poor growth and development?	92.8	86.3	Infants
What are the cost and cost–effectiveness of specially formulated foods (SFFs) and other dietary interventions?	92.5	88.7	Moderate
What are the most effective interventions in humanitarian contexts to prevent wasting and nutritional oedema?	92.1	87.1	Prevention
What is the cost–effectiveness of integrating moderate wasting into the primary healthcare system (in places where moderate wasting is managed outside the health system)?	92.0	89.3	Moderate
What tools, support systems, etc. can be utilized to maximize effectiveness of community health workers (CHWs) management?	91.9	86.8	Severe
Which infants and children with moderate wasting should be prioritized for supplementation based on risk factors?	91.8	87.4	Moderate
What are the cost and cost–effectiveness of different quantities of ready-to-use therapeutic food (RUTF)?	91.8	88.1	Severe
Which interventions are effective to prevent relapse and improve long-term health and development outcomes in infants and children with moderate wasting?	91.7	87.1	Moderate
What are the cost and cost–effectiveness of preventive interventions for wasting and nutritional oedema compared to each other?	91.5	84.6	Prevention
Which tools and strategies can health workers use to assess and manage simple breastfeeding problems effectively?	91.5	85.7	Infants
Would infants and children with moderate wasting who do not meet criteria for prioritization with specially formulated foods (SFFs) in low-risk settings benefit from a dietary intervention?	91.4	83.6	Moderate
What intervention packages to support existing health staff, such as using peer counsellors for the assessment and management of breastfeeding/lactation difficulties exist and how do they compare?	91.2	84.7	Infants
What are the most effective and cost–effective targeting strategies for the provision of specially formulated foods (SFFs) for moderate wasting in humanitarian settings?	90.7	83.7	Moderate
What is the effectiveness of different types of formulas including F-75, diluted F-100, full-strength F-100, and infant formulas (potentially consider pre-term formulas if appropriate) as well as donor human milk in inpatient settings for infants less than 6 months of age at risk of poor growth and development, as well as those with severe wasting and/or nutritional oedema specifically?	90.7	84.9	Infants
What are the cost and cost–effectiveness of managing moderate wasting using available home foods in different contexts?	90.6	85.0	Moderate
How should infants less than 6 months of age at risk of poor growth and development who fail to respond to initial supported breastfeeding and clinical treatment be managed?	90.5	83.2	Infants

Research question	RPS	AEA	Population
Which interventions are effective to prevent relapse and improve long-term health and development outcomes in infants and children with severe wasting and/or nutritional oedema?	90.1	84.8	Severe
What is the cost–effectiveness of interventions for prevention of wasting and nutritional oedema, including logistics and implementation costs?	90.0	83.3	Prevention
What is the effectiveness of community health workers (CHWs) in management of moderate wasting throughout the care pathway?	89.8	84.8	Moderate
What are the most effective and cost–effective platforms or services to implement food-based interventions for prevention of wasting and nutritional oedema?	89.5	81.2	Prevention
What is the potential role of cash programming in prevention of wasting and nutritional oedema, in isolation or in combination with other interventions?	89.5	83.3	Prevention
What are the risk factors (individual, household, community, programme-level) for relapse to moderate wasting?	89.2	81.4	Moderate
What chronic conditions are associated with non-response or treatment failure in infants and children with severe wasting and/or nutritional oedema?	89.2	82.1	Severe
What are the cost and cost–effectiveness of alternative ready-to-use therapeutic food (RUTF) formulations in different settings?	89.0	80.4	Severe
What low-cost and scalable livelihood initiatives can build resilience against wasting and nutritional oedema?	89.0	82.0	Prevention
What are the risk factors (individual, household, community, programme-level) for relapse to severe wasting and/or nutritional oedema?	88.9	83.2	Severe
What screening criteria should be used to detect infants less than 6 months of age at risk of poor growth and development in the community?	88.8	82.2	Infants
Which packages of care are most effective at improving outcomes in infants less than 6 months of age at risk of poor growth and development and preventing wasting and nutritional oedema in these infants?	88.8	84.6	Infants
What tools, support systems, etc. can be utilized to maximize effectiveness of community health workers (CHWs) management?	88.6	82.0	Moderate
What is the effectiveness of other types of prevention interventions apart from small-quantity lipid-based nutrient supplements (SQ-LNS) and medium-quantity lipid-based nutrient supplements (MQ-LNS) for prevention of wasting and nutritional oedema?	88.6	77.9	Prevention
What is the effectiveness of community health workers (CHWs) in management of severe wasting and/or nutritional oedema throughout the care pathway?	88.6	80.9	Severe
What is the cost–effectiveness of community health workers (CHWs) for management of severe wasting and/or nutritional oedema and the impacts of this approach on coverage and other services?	88.6	80.9	Severe
What is the effectiveness of different approaches to dietary management of moderate wasting, including the use of available home foods in different contexts?	88.5	79.9	Moderate
What are the acceptability and existing practices around wet nursing, supplementary suckling technique, re-establishment of breastfeeding, etc.?	88.5	81.8	Infants
What prioritization criteria can be used for infants less than 6 months of age at risk of poor growth and development if caseloads are high and resources limited?	88.4	81.2	Infants
What is the effectiveness of social interventions, psychosocial support, and mental health for mothers/caregivers of infants and children with severe wasting and/or nutritional oedema?	88.4	83.2	Severe

Research question	RPS	AEA	Population
What is the cost–effectiveness of community health workers (CHWs) for management of moderate wasting and the impacts of this approach on coverage and other services?	88.3	81.1	Moderate
What are the cost and cost–effectiveness of psychosocial stimulation interventions for infants and children with severe wasting and/or nutritional oedema, including the costs for caregivers and trained staff?	88.3	82.0	Severe
What are the priority medical and nutritional support and interventions for mothers/caregivers of infants less than 6 months of age at risk of poor growth and development?	87.9	80.7	Infants
What is the feasibility of implementation and effectiveness of interventions aimed at addressing maternal mental health among mothers/caregivers of infants less than 6 months of age at risk of poor growth and development?	87.8	79.8	Infants
What is the need for and the effectiveness of supplemental milk and breastmilk fortifiers predominantly in inpatient settings for infants less than 6 months of age at risk of poor growth and development, as well as those with severe wasting and/or nutritional oedema specifically?	87.5	80.3	Infants
What are the best approaches to develop and implement context-specific interventions using home-based foods/interventions, apart from specially formulated foods (SFFs), for the management of moderate wasting?	87.5	80.3	Moderate
What are the effectiveness and cost–effectiveness of weekly versus fortnightly visits during management of severe wasting and/or nutritional oedema?	87.4	79.4	Severe
What are the optimal quantity, duration and timing of food-based interventions for prevention of wasting and nutritional oedema?	87.4	80.7	Prevention
What are the energy/nutrient requirements of infants and children with severe wasting and/or nutritional oedema, including when children improve from severe to moderate wasting?	86.9	78.5	Severe
What are appropriate methods and tools for monitoring and improving early childhood development in primary and secondary care for infants less than 6 months of age at risk of poor growth and development?	86.8	80.0	Infants
What interventions/approaches increase treatment coverage for infants and children with severe wasting and/or nutritional oedema?	86.8	80.6	Severe
What is the effectiveness of different novel (e.g. low or no-milk) ready-to-use therapeutic food (RUTF) in the management of severe wasting and/or nutritional oedema?	86.7	78.9	Severe
How can infants less than 6 months of age at risk of poor growth and development be identified across settings?	86.7	76.1	Infants
What are the direct, indirect, and opportunity costs to families of food-based interventions for prevention of wasting and nutritional oedema?	86.6	74.7	Prevention
What are effective interventions (e.g. dietary, other) that can be provided in the absence of ready-to-use therapeutic food (RUTF) for the management of severe wasting and/or nutritional oedema?	86.6	82.1	Severe
Can SQ-LNS prevent or reduce relapse to moderate wasting?	86.5	79.7	Moderate
What pathogens (e.g. cryptosporidium) drive diarrhoea-related mortality in hospitalized children with severe wasting and/or nutritional oedema, and how can they be addressed?	86.5	81.7	Severe
For infants and children with severe wasting and/or nutritional oedema who are growing but do not reach the recovery within the maximum length of stay for a programme, is it feasible for them to be kept longer under treatment?	86.3	78.6	Severe

Research question	RPS	AEA	Population
What are the potential impacts of maternal interventions in the context of prevention of wasting and nutritional oedema?	86.0	78.6	Prevention
What is the optimal rate of weight gain in infants and children with severe wasting and/or nutritional oedema?	85.9	80.6	Severe
What is the impact of post-exit cash transfers combined with individual counselling for mothers/caregivers of infants and children with severe wasting and/or nutritional oedema?	85.8	78.7	Severe
What are the cadres, training needs, and tools that can most effectively support breastfeeding?	85.8	75.8	Infants
What are the early markers of likelihood of non-recovery from severe wasting and/or nutritional oedema?	85.8	76.7	Severe
What is the optimal antibiotic regimen for infants and children with wasting and/or nutritional oedema?	85.8	77.9	Severe
What are the energy/nutrient requirements of infants and children with moderate wasting?	85.7	79.2	Moderate
What is the effectiveness of social protection programmes and approaches (e.g. maternity/paternity leaves; cash support; financial compensation for parental leaves) for prevention of wasting and nutritional oedema?	85.7	78.7	Prevention
Can SQ-LNS prevent or reduce relapse to severe wasting and/or nutritional oedema?	85.7	78.3	Severe
What is the effectiveness of interventions targeting social, psychological, and economic challenges faced by mothers/caregivers of infants less than 6 months of age at risk of poor growth and development?	85.2	78.1	Infants
Should management of nutritional oedema differ from management of severe wasting?	85.2	80.8	Severe
What is the cost–effectiveness of cash transfers (based on metrics such as disability-adjusted life years) and the impact of this intervention in different settings for mothers/caregivers of infants and children with severe wasting and/or nutritional oedema?	85.1	76.3	Severe
What approaches are most effective to re-establish breastfeeding for mothers of infants less than 6 months of age at risk of poor growth and development who have stopped breastfeeding?	84.8	75.3	Infants
What are the drivers of early cessation of breastfeeding in infants less than 6 months of age at risk of poor growth and development and what could be done to prevent early cessation?	84.8	76.0	Infants
What is the optimal micronutrient content of specially formulated foods (SFFs)?	84.7	76.6	Moderate
What are the effects of different integrated post-exit packages in infants and children with severe wasting and/or nutritional oedema?	84.6	75.7	Severe
How should infants less than 6 months of age at risk of poor growth and development be best linked with related services (e.g. Integrated Management of Newborn and Childhood Illness, immunizations, growth monitoring, mental health, disability treatment services)?	84.5	75.3	Infants
What would be the impact of interventions that combine nutrition interventions (e.g. SFFs) with interventions for prevention/management of infections (e.g. malaria, respiratory infections, diarrhoeal disease), for both prevention and management of wasting and nutritional oedema?	84.5	72.8	Prevention
What is the optimal management strategy for infants and children with severe wasting and/or nutritional oedema and with dehydration, circulatory impairment, and shock?	84.4	78.4	Severe

Research question	RPS	AEA	Population
What are the most appropriate methods and tools for assessing breastfeeding, including whether an infant less than 6 months of age is being exclusively breastfed, having difficulties breastfeeding, etc.?	84.4	73.4	Infants
What are the effects of combining psychosocial stimulation with other interventions in infants and children with moderate wasting?	84.3	76.4	Moderate
What are the pathways underlying mortality in infants less than 6 months of age at risk of poor growth and development?	84.0	71.8	Infants
What is the effectiveness of ReSoMal compared to low-osmolarity ORS without added potassium in infants and children with severe wasting and/or nutritional oedema?	83.9	76.8	Severe
What field-friendly, low-cost tools for screening, identification, and referral can be used to best support infants and children with severe wasting and/or nutritional oedema who are not responding to treatment?	83.8	78.2	Severe
What are the effects of a package of interventions for the prevention of wasting and nutritional oedema that includes maternal and infant and young child feeding (IYCF) counselling?	83.7	75.5	Prevention
How can maternal interventions be improved to enhance breastmilk quality and quantity for infants less than 6 months of age at risk of poor growth and development?	83.6	73.7	Infants
Which community, household and child-level factors are associated with likelihood of progressing to wasting or nutritional oedema?	83.5	74.1	Prevention
What are the maximal duration and optimal duration that treatment should take for severe wasting and/or nutritional oedema?	83.3	76.8	Severe
What are the most effective and cost–effective household and geographical targeting criteria to implement preventive specially formulated foods (SFFs) for prevention of wasting and nutritional oedema?	83.3	75.6	Prevention
How can caregivers be better supported in providing home-based meals that prevent wasting and nutritional oedema?	83.3	73.0	Prevention
Are different preventive strategies needed for infants and children who are 6–23 months of age compared to children who are 24–59 months of age?	82.8	73.0	Prevention
What are the effects of combining psychosocial stimulation with other interventions in infants and children with severe wasting and/or nutritional oedema?	82.8	73.4	Severe
Does inpatient care for infants less than 6 months of age at risk of poor growth and development improve outcomes compared to outpatient care, based on a set of criteria or different factors?	82.6	74.9	Infants
What is the optimal rate of weight gain in infants and children with moderate wasting?	82.6	76.5	Moderate
What are potential adverse effects of specially formulated foods (SFFs) for prevention of wasting and nutritional oedema, including displacing breastfeeding and home diets, encouraging consumption of processed foods, and displacing healthy food production and preparation skills?	82.5	78.0	Prevention
How can F-75 be revised to best meet the needs of children with nutritional oedema?	82.5	74.7	Severe
How can infants and children with severe wasting and/or nutritional oedema and underlying medical conditions and/or disability be managed?	82.3	73.0	Severe
What are the impacts of maternal, infant and young child feeding (IYCF) counselling/interventions on improved practices and on the prevention of wasting and nutritional oedema?	82.2	75.5	Prevention

Research question	RPS	AEA	Population
What is the response to interventions in infants and children with moderate wasting who have specific risk factors?	82.0	71.6	Moderate
What are the optimal compositions of F-75, F-100, and RUTF for severe wasting and/or nutritional oedema?	81.9	74.3	Severe
What are the pathways underlying mortality in infants and children with severe wasting and/or nutritional oedema?	81.8	72.7	Severe
What are implementation considerations for psychosocial stimulation including intensity and frequency, as well as who can provide the intervention and in what contexts, for infants and children with moderate wasting?	81.7	71.8	Moderate
What is the optimal duration and timing of preventive interventions to prevent wasting and nutritional oedema?	81.7	68.6	Prevention
What are social factors that may be associated with the risk of poor outcomes in children with severe wasting and/or nutritional oedema?	81.6	72.6	Severe
What is the prevalence of refeeding syndrome and optimal management of refeeding syndrome in infants and children with severe wasting and/or nutritional oedema in inpatient settings?	81.5	71.1	Severe
What are the pathways underlying mortality in infants and children with moderate wasting?	81.5	71.6	Moderate
What are the specific causes of nutritional oedema?	81.4	74.3	Severe
How should hydration status in infants and children with severe wasting and/or nutritional oedema be assessed and classified?	81.3	75.8	Severe
What are the optimal and feasible enrolment and monitoring/transfer criteria to best identify infants less than 6 months of age at risk of poor growth and development across different settings?	81.3	69.9	Infants
What are the drivers of the use of prelacteal feeds in infants less than 6 months of age at risk of poor growth and development?	81.3	70.6	Infants
What is the quality-adjusted coverage/effective coverage of management of wasting and nutritional oedema?	81.0	72.1	Severe
What is the optimal antibiotic regimen for infants and children with moderate wasting?	80.9	72.3	Moderate
What are implementation considerations for psychosocial stimulation including intensity and frequency, as well as who can provide the intervention and in what contexts, for infants and children with severe wasting and/or nutritional oedema?	80.8	73.7	Severe
What are the cost and cost–effectiveness of psychosocial stimulation interventions for infants and children with moderate wasting, including the costs for caregivers and trained staff?	80.7	69.7	Moderate
What is the optimal quantity and packaging of ready-to-use therapeutic food (RUTF) from a usage/user perspective?	80.7	73.2	Severe
Does inpatient care of children with severe wasting and/or nutritional oedema with specific risk factors improve outcomes compared to outpatient care?	80.6	73.4	Severe
What are the impacts of services and how these services are delivered focusing on infants less than 6 months of age at risk of poor growth and development?	80.6	67.4	Infants
What are the effects of donor human milk and hydrolyzed and lactose-free feeds for infants and children with severe wasting and/or nutritional oedema who are not tolerating F-75 or F-100?	80.5	74.2	Severe
What is the effectiveness of different types of formulas in infants less than 6 months of age at risk of poor growth and development who have already stopped exclusive breastfeeding?	80.2	71.8	Infants

Research question	RPS	AEA	Population
What is the feasibility and sustainability of blanket compared to targeted approaches across settings for prevention of wasting and nutritional oedema?	79.6	66.8	Prevention
What is the relationship between wasting and stunting?	79.3	67.9	Severe
Can adding potassium and/or sodium to F-75 achieve optimal content for infants and children with severe wasting and/or nutritional oedema?	79.2	72.0	Severe
What is the efficacy of antibiotics (apart from daily oral co-trimoxazole prophylaxis) with different durations provided to infants and children with severe wasting and/or nutritional oedema as post-discharge interventions?	79.0	70.6	Severe
What are the factors affecting resilience and cognitive development of infants less than 6 months of age at risk of poor growth and development?	79.0	62.4	Infants
What is the optimal delivery of maternal, infant and young child feeding (IYCF) counselling/interventions and the types/models of counselling that are most effective for prevention of wasting and nutritional oedema?	78.9	67.7	Prevention
What are optimal minimum standards for monitoring and improving quality of interventions for infants less than 6 months of age at risk of poor growth and development?	78.9	66.8	Infants
What other electrolyte imbalances affect hospitalized children with severe wasting and/or nutritional oedema?	78.6	66.6	Severe
What are the optimal standardized criteria of feeding intolerance in infants and children with severe wasting and/or nutritional oedema?	78.1	68.4	Severe
Could complementary foods or therapeutic foods be introduced while infants at risk of poor growth and development are less than 6 months of age?	77.7	71.2	Infants
What are the most appropriate methods and tools for assessing and supporting breastfeeding, including relactation where needed and possible for infants and children aged over 6 months and up to 2 years?	77.5	69.5	Severe
What are the most effective approaches to ensure that infants less than 6 months of age at risk of poor growth and development are breastfed in critical situations?	77.3	63.8	Infants
What is the effectiveness of routine amoxicillin and other antibiotics for infants less than 6 months of age at risk of poor growth and development?	77.1	65.7	Infants
Does urine specific gravity help determine the hydration status of infants and children with severe wasting and/or nutritional oedema who presented with dehydration?	77.1	66.1	Severe
What are effective, safe, and culturally-adaptable treatment strategies for managing severe wasting and/or nutritional oedema in infants and children with concurrent metabolic disorders or food allergies (e.g. lactose intolerance, phenylketonuria)?	77.0	66.5	Severe
What is the feasibility of reaching all infants and children with moderate wasting who require specially formulated foods (SFFs) in a variety of contexts?	76.6	67.3	Moderate
What are appropriate methods and tools for monitoring and improving early child development in primary and secondary care for infants and children with severe wasting and/or nutritional oedema?	76.5	69.4	Severe
What are appropriate methods and tools for monitoring and improving early child development in primary and secondary care for infants and children with moderate wasting?	76.3	64.7	Moderate
What is the effectiveness of maternal, infant and young child feeding (IYCF) counselling/interventions on prevention of wasting and nutritional oedema in areas with different levels of wasting and food insecurity?	76.2	67.5	Prevention

Research question	RPS	AEA	Population
What is the prevalence of feeding intolerance to therapeutic milks and lactose intolerance in infants and children with severe wasting and/or nutritional oedema in inpatient settings?	75.9	61.9	Severe
Can somatic hydrolysis be used in existing F-75 formulas to create a hydrolyzed F-75 for infants and children with severe wasting and/or nutritional oedema?	75.5	66.2	Severe
What is the relationship between household food insecurity and wasting and nutritional oedema?	75.1	67.2	Prevention
What are effective, safe, and culturally-adaptable treatment strategies for managing moderate wasting in infants and children with concurrent metabolic disorders or food allergies (e.g. lactose intolerance, phenylketonuria)?	75.0	61.0	Moderate
What are the long-term effects of different types and durations of specially formulated foods (SFFs)?	74.4	65.0	Moderate
What are the impacts of specially formulated foods (SFFs) for prevention of wasting and nutritional oedema on body composition, neurodevelopment, and long-term health outcomes?	74.2	65.9	Prevention
What are the factors affecting resilience and cognitive development of infants and children who have experienced severe wasting and/or nutritional oedema?	73.4	56.8	Severe
How can it be determined whether breastmilk production is below an infant's needs at different ages up to 6 months of age?	72.9	59.0	Infants
What is the effectiveness of probiotic supplementation for infants less than 6 months of age at risk of poor growth and development?	72.5	60.0	Infants
What is the pathophysiology of severe wasting and nutritional oedema?	71.0	58.6	Severe
How should hydration status in infants and children with moderate wasting be assessed and classified?	70.3	59.8	Moderate
What are the impacts of preventive interventions on equity in different contexts?	69.0	53.9	Prevention
What are the long-term cardiometabolic effects and other consequences of ready-to-use therapeutic food (RUTF)?	68.6	57.8	Severe
Should a renal function test be a requirement before starting therapeutic milks in infants and children with severe wasting and/or nutritional oedema?	68.1	59.6	Severe
How can health workers differentiate between nutritional causes of oedema and other underlying conditions when detected in a community setting?	68.1	60.4	Severe
What is the pathophysiology of moderate wasting?	67.6	58.2	Moderate

AEA: average expert agreement; RPS: research priority score; RUTF: ready-to-use therapeutic food; SFFs: specially formulated foods; CHW: community health worker; SQ-LNS: small-quantity lipid-based nutrient supplement; MQ-LNS: medium-quantity lipid-based nutrient supplements; ORS: oral rehydration solution; IYCF: infant and young child feeding

For more information, please contact:

Department of Nutrition and Food Safety
World Health Organization
Avenue Appia 20 1211 Geneva 27 Switzerland
Email: nfs@who.int