

In support of
NO WASTED LIVES



THE RESEARCH AGENDA FOR ACUTE MALNUTRITION REVISITED

FEBRUARY 2021

In January 2018, the Council of Research & Technical Advice on Acute Malnutrition (CORTASAM) and the No Wasted Lives Coalition published a global [Research Agenda](#) for Acute Malnutrition, outlining seven priority research areas to drive the use of evidence to support scale-up and impact for children with wasting¹ globally. This Research Agenda included an initial mapping of the evidence conducted in 2017 to identify outstanding research questions and needs in each area as well as outcomes to be achieved by 2020.

In 2019, recognising the progress of significant research efforts since the original Research Agenda was released, CORTASAM initiated a Research Landscape Review to evaluate progress made towards the outcomes specified in the Research Agenda which was published in 2020. The objectives of the Landscape Review were to:

1. Review completed, ongoing, or planned research in the seven research priority areas of the Research Agenda, building on the original mapping of evidence and focusing on new efforts since 2017; and
2. Evaluate outstanding research needs and progress made to date towards the 2020 outcomes specified in the Research Agenda.

The Landscape Review was not intended to be a systematic review of all research and evidence in the priority areas. Rather, the Landscape Review can be considered an integrative review with elements of a semi-systematic review aiming to provide an overview of a research area, including developments over time, and to create a critical narrative of research progress and outstanding gaps in each area. This review process involved literature reviews and technical consultations. Details on the methodology of the Landscape Review can be accessed [here](#).

The results of the Landscape Review on completed, ongoing, and planned research in the priority research areas can be accessed [here](#). On the basis of these results, the members of CORTASAM have evaluated developments in the research areas, progress towards the 2020 outcomes specified in the Research Agenda, and outstanding gaps that need to be filled to achieve these outcomes. This document details recommendations on research priorities, emerging evidence, and outstanding needs to support evidence-based programmes and normative guidance. In addition to supporting the ongoing process of developing comprehensive guidelines on wasting at the World Health Organization (WHO), these recommendations also aim to support and provide complementarity to ongoing efforts for operational alignment through the United Nations (UN) Global Action Plan on Child Wasting and application of evidence for nutrition programming in the context of the COVID-19 pandemic.

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The authors alone are responsible for the views expressed in this statement and they do not necessarily represent the decisions, policy or views of their organisation.

1 While the term 'wasting' will be predominantly used in this report, there are sources cited that use the term 'acute malnutrition' as this was the predominant terminology used at the time of publication of the original Research Agenda. Both 'wasting' and 'acute malnutrition' are defined here as weight-for-height z-score (WHZ) <-2, nutritional oedema and/or mid-upper arm circumference (MUAC) <125mm.

2 And with further comments from Zita Weise Prinzo (World Health Organization), Noël Marie Zagre (UNICEF West Africa Regional Office), and Purnima Menon (International Food Policy Research Institute).

EXECUTIVE SUMMARY

Significant progress has been made against the Council's original recommendations for the research priority areas first identified in 2018 but gaps still exist. Key recommendations for further research along with brief summaries of the different research areas and are mentioned below. More details on the results of the Landscape Review and identified research needs for each individual research priority area are provided in the following sections.

STRENGTHEN THE INTEGRATION OF COMMUNITY-BASED APPROACHES TO MANAGEMENT OF WASTING BEYOND HEALTH FACILITIES WITH OTHER LEVELS OF HEALTH SYSTEMS

There is growing evidence and a large body of ongoing research on the involvement of Community Health Workers (CHWs) for management of severe wasting, which is encouraging. However, evidence is needed with regards to whether CHWs can diagnose and manage moderate wasting. More evidence, particularly from implementation research, is also needed on best practices to support scale-up of involvement of CHWs in the management of severe wasting across contexts. This should include exploring optimal levels and modalities of supervision and training for CHWs to achieve quality care, rational and targeted use of the community health workforce in health systems integration, and the role of CHWs in multisectoral approaches that prevent and address underlying causes of wasting.

EXPAND THE EVIDENCE BASE FOR SIMPLIFIED APPROACHES ACROSS CONTEXTS

There is a proliferation of research and operational pilots in non-emergency settings using simplified protocols that base admission and discharge on mid-upper arm circumference (MUAC) (+ oedema), combine treatment of severe and moderate wasting, use one product for management of moderate and severe wasting and/or change standard RUTF dosage protocols for treatment of severe wasting. While results from these studies will expand the evidence base, more research is needed across contexts, particularly from outside of sub-Saharan Africa.

TOOLS AND APPROACHES FOR DETECTING AND DIAGNOSING CHILDREN WITH WASTING

Basing admission and discharge on MUAC is a common component of simplified approaches. However, the consequences of the single-criteria approach need to be further evaluated, including number of children at risk of malnutrition-related mortality not identified and consequences for risks of relapse. Additional approaches that can be used to identify children at risk of mortality need to be explored. These include screening with weight-for-age, using MUAC at shorter intervals, context- and gender-specific MUAC thresholds and non-anthropometric indicators of risk.

EXPAND EVIDENCE BASE FOR REDUCED RUTF DOSAGE SCHEDULES

There is an expanding evidence base on different RUTF dosage schedules that reduce the amount of product required per course of treatment. However, to draw robust conclusions about the safety and effectiveness of reduced dosage schedules, more research is needed across contexts, particularly from outside of sub-Saharan Africa, on short term and longer-term outcomes (including impact on height, body composition and other non-anthropometric outcomes) as well as on effects among different age groups and vulnerable populations.

RESEARCH ON FLUID MANAGEMENT IN SEVERELY WASTED CHILDREN

Recent reviews highlighted that global guidelines on fluid management in children with severe wasting may need updating. Further research is needed on what fluids to use in which circumstances and on adequate volumes and routes of administration. Specifically, some studies suggest that the recommended use of ReSoMal may be inappropriate for oral fluid management in severely wasted children and evidence from South Asia suggests that ReSoMal can be replaced by oral rehydration solution (ORS). However, more evidence on ORS for rehydration is required from sub-Saharan African settings. Moreover, research is required on whether more aggressive intravenous (IV) rehydration approaches are appropriate for severely wasted children with severe dehydration and/or shock since a recent review found that withholding IV fluids may leave children dehydrated.

DEVELOP A STANDARDISED DEFINITION OF POST-TREATMENT RELAPSE AND A CONCEPTUAL FRAMEWORK IN ORDER TO SUPPORT EVIDENCE GENERATION

There is no standard definition of post-treatment relapse to moderate or severe wasting and no consistent measurement across research or programme monitoring. As a result, the burden of and risk factors for relapse across contexts continues to be poorly understood. In order to support evidence generation, CORTASAM has proposed interim guidance for a standardised definition of relapse and regression to and reoccurrence of wasting after receiving treatment, for both research and programmes and called for feedback from researchers and practitioners with the aim to update it as new evidence emerges³. In addition, CORTASAM has developed a conceptual framework for relapse with the objective to support the development and testing of effective interventions to reduce post-treatment relapse. There is a large body of ongoing and planned research on relapse. This research should reflect the latest guidance on definitions and measurement.

EVIDENCE ON AND UPTAKE OF TOOLS AND APPROACHES TO IDENTIFY AND MANAGE NUTRITIONALLY AT-RISK MOTHERS AND INFANTS <6 MONTHS OF AGE (MAMI) ACROSS CONTEXTS

There has been significant progress made in approaches to manage at risk mothers and infants under six months both through the implementation and piloting of the C-MAMI tool in several contexts and more recently with remodelling of the C-MAMI Tool as the MAMI care pathway (available for piloting in 2021). Progress has also been made to build evidence on criteria to identify at risk infants using both weight-for-age (WAZ) and mid upper arm circumference (MUAC) as well as feeding, clinical and maternal indicators.

There remains a need for coordinated, evidence-based global guidance informed by multiple contexts for countries to effect the necessary institutional, policy and system development required to advance case identification and management and inform and drive policy and programming development. To this end coordinated formal and operational research, from a range of contexts including South Asia, is needed to increase the strength of evidence on case definition and approaches to identify and manage infants at risk. Active engagement in WHO guideline development process, engagement with and across sectors including health, early childhood development, maternal mental health and neonatal health as well as dissemination of evidence through global and regional networks is also key. This is being actively pursued by the MAMI Global Network⁴.

RESEARCH ON ALTERNATIVE FORMULATIONS

In recent years, several studies have investigated the effectiveness of alternative formulations of RUTF including those that aim at replacing or reducing milk and/or peanut content or change the fatty acid profile of RUTF. A systematic review on safety and effectiveness of RUTF with reduced milk protein content, coordinated by WHO, has recently been carried out (in press) with the aim to inform a new guideline on dairy protein content in RUTF (underway). Research gaps identified by WHO in this process should be prioritised. In addition, any future studies on alternative formulations should include evaluation of costs, cost-effectiveness, acceptability, body composition, long-term growth, neurocognitive outcomes and whether the same product can be used for managing moderate and severe wasting. The role of emulsifiers in RUTF which reduce visible separation of oil but may have harmful effects on gut health should be further investigated. Furthermore, effectiveness of new formulations should be tested in home-based settings at operational scale. Wider economic, health system and environmental implications of alternative formulations should be considered. The role of the private sector in models of development and delivery of RUTF formulations should be examined

³ The Council of Research & Technical Advice for Acute Malnutrition (2020). *Guidance to improve the collecting and reporting of data on relapse in children following treatment in wasting programmes.*

⁴ www.ennonline.net/MAMI

CONCLUSIONS ABOUT BROADER RESEARCH PRIORITIES

While progress has been made towards answering key research questions identified in the global Research Agenda, considerable research gaps remain. Promising interventions and modifications to treatment protocols have too often failed to be tested at scale. The research priority areas identified in the Research Agenda were the result of a formal prioritisation exercise (see [here](#)) and were considered to have the highest potential to reduce morbidity and mortality among wasted children globally.

Significant changes in the research landscape have occurred in recent years. For example, research on simplified approaches to treatment of wasting commonly encompasses research areas that have previously been considered relatively separate. These include expanding admission and discharge criteria to include moderate wasting, simplified and reduced dosage schedules for RUTF in the management of both moderate and severe wasting, and, in some contexts, the involvement of CHWs in the management of wasting. It is important to acknowledge the overlap and opportunities across these different research areas, avoiding siloed thinking, and to summarise the evidence and large body of ongoing work in a unifying way to best inform guidelines and policies.

The Council encourages others involved in research and operational pilots to recognise the overlap between different research areas and widely consider implications on the detection, diagnosis, and management across the continuum of moderate and severe wasting. This also extends to prevention of wasting, which has increasingly become a global public health priority, although research on the causes of wasting and on effective interventions to prevent wasting are limited. The Council therefore encourages more research to recognise the continuum between prevention and treatment of wasting and to explore effective prevention interventions that can reduce the number of cases of wasting at scale. Recent efforts to identify research priorities for the prevention of wasting (see [here](#)) could guide these efforts to build the evidence base. Furthermore, across all research areas, studies should be implemented in under-researched areas and populations, particularly in South Asia. In South Asia, lack of government support often represents a major barrier to wasting programming and research. Further research to understand and overcome these barriers could complement the more technical-focused research. Lack of evidence across contexts represents a major limitation for the development of global guidelines, so improved representation of all populations affected by wasting in research must be a priority.



RESEARCH AREA:**1 EFFECTIVE APPROACHES TO DETECT, DIAGNOSE, AND TREAT ACUTE MALNUTRITION IN THE COMMUNITY****RECAP: OUTSTANDING RESEARCH NEEDS IDENTIFIED IN THE RESEARCH AGENDA**

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

DETECTION:**OUTSTANDING NEEDS**

Further expansion and documentation of the use of MUAC by community members at scale and across contexts

Identification and testing of context-specific MUAC thresholds for detection by community members

TYPE OF EVIDENCE/RESEARCH NEEDED

- Compilation and documentation of existing evidence across contexts.

- Implementation research to refine and expand this model across contexts, including demand generation within the community

- Robust trials to inform policy and guideline development with priority to randomised control trials

DIAGNOSIS & TREATMENT IN THE COMMUNITY:**OUTSTANDING NEEDS**

Further evidence on use of CHWs for diagnosis and treatment in the community across contexts, including appropriate referral of complicated cases

Identification and testing of tools to support the integration of treatment of acute malnutrition into health platforms

TYPE OF EVIDENCE/RESEARCH NEEDED

- Robust trials, with priority to randomised control trials, and cost-effectiveness analyses to demonstrate safety and effectiveness and inform policy and guideline development

- Implementation Research

CHANGES IN THE RESEARCH LANDSCAPE AND RECENTLY EMERGING EVIDENCE

An overview of completed, ongoing, and planned research in this area identified in the Landscape Review can be found [here](#).

There is increasing evidence that CHWs can manage severe wasting in the community at village or household level and have the potential to increase treatment coverage. Cost-effectiveness analyses of completed experimental studies suggest that, if treatment coverage is increased sufficiently, costs per child treated and recovered can be reduced through CHWs compared to standard community-based management of acute malnutrition (CMAM) where RUTF distribution, and check-ups are made at the health facility level. Studies also suggest that costs for beneficiaries can be reduced markedly. A range of experimental and observational studies are ongoing that will generate further evidence on effectiveness, cost-effectiveness, and effects on coverage across different contexts to inform future implementation at scale. Questions remain regarding best practices and the right level and frequency of training, supervision, and support for CHWs. Moreover, most projects using CHWs were implemented at small-scale, integrating management of severe wasting into integrated community case management (iCCM). Broader integration into health systems remains to be demonstrated, although these projects have had an influence on national policies in some settings. There is limited representation of evidence across different contexts, with few studies outside of sub-Saharan Africa. Most studies focus on severe wasting; there is little evidence on the use of CHWs for managing moderate wasting, although at least one study tests the use of CHWs for delivering a combined protocol for moderate and severe wasting.

RECAP: OUTCOMES BY 2020 DEFINED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

More children are diagnosed and treated for acute malnutrition due to 1) an increase in the proportion of children detected and referred from the community; and 2) an increase in the proportion of children who are treated at the household level by community health workers.

POLICY-LEVEL: Global and national guidance supports the use of MUAC as a primary tool and criteria for detection by community members and diagnosis by community health workers, including context-specific thresholds to capture the true burden of children with acute malnutrition. High-burden countries include national-level guidance on treatment in the community at household level where feasible.

OPERATIONAL-LEVEL: Community detection of acute malnutrition is delivered at scale in high-burden countries with clear policies to guide roles and responsibilities for screening and training. High-burden countries are able to successfully implement integrated treatment of acute malnutrition into their health platforms and systems. Communities are mobilised to promote community-based detection, diagnosis, and treatment.

PROGRESS TOWARDS 2020 OUTCOMES

There has been progress in increasing the number of wasted children receiving treatment (increasing from 4.1 million children receiving treatment for severe wasting in 2016 to 5.2 million in 2018²), but it has been slow and gaps in detection, diagnosis, and treatment remain. Availability of approaches to detect and diagnose wasting at the community-level (either through anthropometric or other risk indicators) is a significant gap to accelerate progress. The use of MUAC for detection by community members (“FamilyMUAC”) has rapidly increased in recent years but impact on treatment coverage and scalability are unclear and there is currently no global guidance on the use of MUAC by community members as the primary tool for detection. Further ongoing efforts are exploring non-anthropometric indicators to detect risk of wasting. The evidence base on CHWs for both diagnosis and treatment of severe wasting is expanding and examples of treatment programmes using CHWs are increasing; however, these projects tend to be small and effectiveness at scale remains to be demonstrated. While wasting is increasingly recognised as a continuum encompassing moderate and severe forms, there is also little evidence on using CHWs for managing moderate in addition to severe wasting. There is limited global guidance on CHWs for wasting management, although some progress with countries looking to integrate CHWs for managing wasting into national guidelines for iCCM has been made (e.g. in Mali).

RECOMMENDATIONS FOR FURTHER RESEARCH

Strengthen the evidence on integration of community-based approaches to management of wasting beyond health facilities with other levels of health systems

- More evidence, particularly from implementation research, is needed on best practices to support scale-up of involvement of CHWs in the management of severe wasting across contexts. This should include exploring optimal levels and modalities of supervision and training for CHWs to achieve quality care, rational and targeted use of the community health workforce in health systems integration, and the role of CHWs in multisectoral approaches that prevent and address underlying causes of wasting such as Nurturing Care⁵.
- More evidence is needed from a range of contexts, and contextual factors that may influence the success of management of severe wasting with CHWs need to be evaluated, including aspects of health systems, population health (e.g. levels of wasting and stunting), and admission criteria for wasting programmes. More representation from South Asia is needed.
- Emerging evidence in this area needs to be summarised and considered in the development of guidelines for wasting. So far, research and operational projects on CHWs remain a patchwork without unifying guidelines on best practices to maximise impact.

Expand research on community-based approaches beyond health facilities for management of moderate wasting

- Operational evidence is needed on community-based approaches at the village and household level for the detection, diagnosis, and management of moderate wasting as research on CHWs and other approaches such as FamilyMUAC focus largely on severe wasting. Evidence is needed on whether household members can detect moderate wasting and whether CHWs can be used to diagnose and manage moderate wasting.

Explore tools and indicators for detection and diagnosis of wasting at community-level

- Further research is needed on easy-to-use and accurate tools for detecting wasting by community members and CHWs at the village and household level. This could include innovative changes to MUAC tools (e.g. UniMUAC or mobile phone photo-based applications), particularly for low-literacy CHWs, or approaches to using MUAC (e.g. more frequent screening) and other indicators (e.g. using WAZ and/or non-anthropometric indicators of risk).
- More attention should also be paid to how community members can be informed about and oriented towards tools for detecting and diagnosing wasting, including through multiple communication channels such as local leaders, organized groups, social media, etc.

Differentiate between screening for wasting by community members (households/family) and diagnosis by CHWs

- Family members and CHWs are distinct groups of individuals. FamilyMUAC is an approach for frequent and regular screening of children to detect wasting. It is linked but distinctly different from diagnosis and management of wasting by CHWs. Separate research questions should cover detection of wasting by community members and management of wasting by CHWs.
- Implementation research should evaluate optimal levels of supervision and support of caregivers using MUAC to detect wasting, including how to link FamilyMUAC to support by CHWs.



RESEARCH AREA:**2 APPROPRIATE ENTRY AND DISCHARGE CRITERIA FOR TREATMENT OF ACUTE MALNUTRITION TO ENSURE OPTIMUM OUTCOMES****RECAP: OUTSTANDING RESEARCH NEEDS IDENTIFIED IN THE RESEARCH AGENDA**

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

ENTRY CRITERIA:

OUTSTANDING NEEDS	TYPE OF EVIDENCE/RESEARCH NEEDED
Evidence on expanded MUAC entry criteria and alternative options to identify high risk children that are not identifiable by MUAC	<ul style="list-style-type: none"> ▪ Robust trials, with priority to randomised control trials, and cost-effectiveness analyses ▪ Implementation research
Evidence on simplified protocols and MAM Decision-Tool including expanded entry criteria for treatment, to non-emergency contexts	<ul style="list-style-type: none"> ▪ Robust trials, with priority to randomised control trials, and cost-effectiveness analyses to establish treatment effectiveness in various contexts ▪ Analysis of operational feasibility and supply chain implications

DISCHARGE CRITERIA:

OUTSTANDING NEEDS	TYPE OF EVIDENCE/RESEARCH NEEDED
Evidence on expanded context-specific discharge criteria for both MAM and SAM, including where programmes addressing MAM are not operational.	<ul style="list-style-type: none"> ▪ Development of a standard definition of successful treatment ▪ Exploratory pilot research in contexts where MAM programmes are not operational

SUMMARY OF RECENTLY EMERGING EVIDENCE

An overview of completed, ongoing, and planned research in this area identified in the Landscape Review can be found [here](#).

There is a growing evidence base on simplified approaches that expand admission criteria for treatment to include both moderate and severe wasting, base admission and discharge on mid-upper arm circumference (MUAC) (+ oedema), and use one product for management of moderate and severe wasting. In addition, the use of RUSF for management of both moderate and severe wasting is also being explored in one yet unpublished study⁶. These approaches have been evaluated in a range of high-quality observational studies and randomised controlled trials (RCTs). Studies are largely implemented in sub-Saharan Africa with some diversity in terms of food security and levels of wasting. There is some evidence that MUAC-only admission and discharge may not identify some children at increased risk of wasting-related mortality that are identified by weight-for-height (WHZ); however, there is limited evidence on how to improve MUAC to identify children only identified by WHZ, including with more frequent screening or gender- and context-specific MUAC thresholds. There is some research suggesting that WAZ may be a complementary measure to MUAC for the identification of these high-risk children and some programmes use WAZ as an additional admission criterion.

6 <https://www.acutemalnutrition.org/en/Simplified-Approaches-Chad>.

PROGRESS TOWARDS 2020 OUTCOMES

RECAP: OUTCOMES BY 2020 DEFINED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

POLICY-LEVEL: Global and national guidance supports a cost-effective and feasible protocol for the treatment of acute malnutrition, including expansion of context-specific MUAC thresholds to capture all high risk children and/or simplified protocols.

OPERATIONAL-LEVEL: Clear policies and operational guidance is in place to support the use of expanded thresholds and simplified protocols across emergency and non-emergency contexts. The operational and supply implications are clearly known and used for programme planning.

There is a proliferation of research and operational pilots in non-emergency settings using simplified protocols (some of which is ongoing) that include a range of modifications to existing protocols, including the expansion of admission criteria for wasting treatment to include moderate wasting. However, there is currently no global guidance and few countries have integrated guidance in their national protocols. CORTASAM has previously recommended the use of MUAC as the primary tool in the community for the detection, diagnosis, and discharge of wasted children (see [here](#)). MUAC-only admission and discharge are a common component of simplified approaches. However, there is limited research on context- and gender-specific MUAC cut-off thresholds and no guidance on how to capture all children at increased risk of mortality that may not be admitted into treatment when using single-criteria approaches.

RECOMMENDATIONS FOR FURTHER RESEARCH

Expand the evidence base for simplified approaches across contexts

- While ongoing research projects and operational pilots will markedly expand the evidence base on simplified approaches in non-emergency settings, more research is needed across contexts, particularly from outside of sub-Saharan Africa.
- The implications of this emerging evidence needs to be considered in the development of guidelines for wasting. Interim guidance, including for non-emergency settings, could be developed for regions with a larger evidence base. In addition to, or in absence of, such guidelines, a unifying narrative around simplified approaches is needed. Expanded entry and discharge criteria are one aspect of these approaches and may no longer represent a distinct research area. Rather, they should be considered more broadly as part of research on simplified approaches and research in this area should recognise and acknowledge links to a range of related research areas (including diagnosis and treatment by CHWs, optimal treatment dosage, and risk of relapse).

Tools and approaches for detecting and diagnosing children with wasting

- The consequences of using single-criteria approaches for admission and discharge for wasting treatment in simplified approaches need to be evaluated, including number of children at risk of malnutrition-related mortality not identified and consequences for risks of relapse.
- There has been limited research on how to improve the ability of MUAC to identify children in the community who would have been identified only by WHZ and are at high risk of mortality. In this context, benefits of frequent screening with MUAC, WAZ, and non-anthropometric indicators of risk should be explored. MUAC and WAZ have advantages over WHZ as they can be measured more frequently. MUAC has higher predictive value if measured at shorter time intervals, so frequent screening with MUAC may decrease the number of at-risk children not identified. This advantage of FamilyMUAC (linked with more frequent screening) is less researched, and the optimal frequency of screening for wasting, including with MUAC and WAZ, and effects on risk for mortality and complications should be evaluated.
- More research on context- and gender-specific MUAC cut-off thresholds is required, including implementation research and modelling of consequences of different thresholds.
- This links to broader questions about fragility, i.e. how to best identify children most at risk of mortality, including with non-anthropometric indicators. This should be an important area of future research and guidance. Particularly, it is important to continue researching the combined effects of wasting and stunting on morbidity and mortality.

RESEARCH AREA:**3 REDUCED DOSAGE OF READY-TO-USE FOOD (RUF) FOR TREATMENT OF ACUTE MALNUTRITION****RECAP: OUTSTANDING RESEARCH NEEDS IDENTIFIED IN THE RESEARCH AGENDA**

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

REDUCED RUTF/RUSF DOSAGE:**OUTSTANDING NEEDS**

Evidence on the safety and effectiveness of reduced dosage of RUTF/RUSF for treatment across contexts

TYPE OF EVIDENCE/RESEARCH NEEDED

- Robust trials, with priority to randomised control trials, and cost-effectiveness analyses to establish safety and effectiveness of new dosages
- Analysis and modelling of operational feasibility and supply chain implications

SUMMARY OF RECENTLY EMERGING EVIDENCE

An overview of completed, ongoing, and planned research in this area identified in the Landscape Review can be found [here](#).

Several robust observational and experimental studies that change standard RUTF dosage protocols for treatment of severe wasting have been recently completed. The MANGO study⁷ was a RCT in Burkina Faso that found overall non-inferior weight gain between the standard and reduced RUTF dosage from admission to discharge. However, a reduced weight gain velocity was observed after two weeks of treatment when the dosage was reduced. The MANGO study also found lower height gain among children receiving the reduced dosage but the clinical significance of this is unclear. A recent retrospective cohort study based on data from two studies in Sierra Leone, found that transitioning to an optimised fixed dose of 500Kcal per day of RUTF of SAM children when MUAC reaches >11.4cm compared to a standard dosage of 175 kcal/kg/d found no difference in weight gain, MUAC gain or relapse to severe wasting but a slower height gain⁸. The OptiMA strategy in Burkina Faso, which gradually reduced RUTF dosage based on weight and MUAC, found lower recovery among children with MUAC<115mm (n=824, recovery: 70.4%) compared to children with MUAC 115-119mm (n=1070, 84.1%) and MUAC 120-124mm (n=3064, 91.4%)⁹. The reduced dosage may have contributed to sub-optimal recovery, so the dosage table was amended and is currently being tested in subsequent studies, although other factors could have contributed to low recovery. Furthermore, the ComPAS trial found that combined management for moderate and severe wasting is non-inferior to standard care. In this study the amount of sachets of ready-to-use foods used to reach full recovery in a child with SAM was lower in the combined protocol (122 versus 193 sachets), compared to the standard protocol¹⁰. Several other studies are ongoing or have been recently completed. Studies are largely implemented in sub-Saharan Africa. Questions remain regarding longer-term impact of reduced dosage, including on height, body composition, and risk of relapse.

7 Kangas ST, Salpéteur C, Nikiéma V, Talley L, Ritz C, Friis H, Briend A, Kaestel P. Impact of reduced dose of ready-to-use therapeutic foods in children with uncomplicated severe acute malnutrition: A randomised non-inferiority trial in Burkina Faso. *PLoS Med*. 2019 Aug 27;16(8):e1002887

8 Stephenson KB, Agapova SE, Taylor Hendrixson D, Koroma AS, Manary MJ. An optimized Dose of Therapeutic Feeding Results in Non-Inferior Growth in Mid-Upper Arm Circumference Compared to Standard Dose in Sierra Leone Recovering from Acute Malnutrition [accepted manuscript]. *Current developments in Nutrition*; 2021 Feb 01; zab007, <https://doi.org/10.1093/cdn/nzab007>

9 Daures M, Phelan K and Issoufou M ; Kou ; a S ; Sawadogo O ; Issaley K ; Cazes C ; Séri B ; Ouaro B ; Akpakpo B ; Mendiboure V ; Shepherd S ; Becquet R;. (2020). New approach to simplifying and optimising acute malnutrition treatment in children aged 6–59 months: the OptiMA single-arm proof-of-concept trial in Burkina Faso. *Br J Nutr*. 2020 Apr 14;123(7):756-767

10 Bailey, J., Opondo, C., Lelijveld, N., Marron, B., Onyo, P., Musyoki, E., Adongo, S., Manary, M., Briend, A., Kerac, M., 2020. A simplified, combined protocol versus standard treatment for acute malnutrition in children 6-59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan. *PloS Medicine* 17, e1003192.

PROGRESS TOWARDS 2020 OUTCOMES

RECAP: OUTCOMES BY 2020 DEFINED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

The overall cost of product required to successfully treat a child with acute malnutrition is reduced, resulting in an overall reduction in the cost of treatment and expansion of programmes using existing resources.

POLICY-LEVEL: Global and national guidance supports a safe and effective reduced dosage schedule for the treatment of acute malnutrition.

OPERATIONAL-LEVEL: Clear policies and operational guidance are in place to support a reduced dosage schedule across programmes at scale.

The evidence base on different RUTF dosage schedules that decrease the amount of treatment product consumed is increasing, (see above), but more evidence is needed. There is no global guidance on safe and effective reduced dosage of RUTF and reduced dosage schedules are not being implemented at scale. There is limited information on effects of reduced dosage on body composition as well as cost-effectiveness and cost reductions but some work in this area ongoing.

RECOMMENDATIONS FOR FURTHER RESEARCH

Expand evidence base for reduced RUF dosage schedules

- To draw robust conclusions about the safety and effectiveness of reduced dosage schedules, more research is needed across contexts, particularly from outside of sub-Saharan Africa, on longer-term outcomes, and on effects among different age groups and vulnerable populations, taking into account different levels of wasting and stunting.

Long-term impact of reduced RUF dosage schedules

- The negative impact of reduced dosage on reduced linear growth, as seen in the MANGO and Sierra Leone studies, and the clinical implications of the lower height gain in the reduced dosage study group requires further investigation.
- There are also questions more generally about the impact of high fat content of RUTF and the risk of obesity in later life. This question of negative impact of high-fat foods on longer-term growth and outcomes could be evaluated in a systematic review, covering not only treatment of wasting but also the broader picture on the role of high-fat foods as a cause for overweight and obesity.

Secondary outcomes of reduced RUF dosage schedules

- Related to questions about height differences, other secondary outcomes, including body composition, need to be considered.
- Costs and cost-effectiveness of reduced dosages in a range of treatment packages need to be evaluated as this is a main driver behind the reduction of RUTF dosage.
- The implications of sharing of RUTF within households, and even selling of RUTF, should be explored in the context of reduced dosage, as this could affect effectiveness of treatment, particularly for vulnerable and food-insecure populations.

Reduced RUF dosage schedules and simplified approaches

- Reduced dosage is often implemented in simplified protocols that include simplified dosage schedules and one product for management of moderate and severe wasting. Therefore, there are links to other research areas and it needs to be considered if reduced dosage should be a distinct research area or a sub-question under the simplified protocol umbrella. Research should acknowledge these links to other research areas.
- Considering reduced dosage schedules under a broader simplified protocol umbrella may be particularly relevant for evaluating consequences for costs of treatment programmes. For instance there are cost implications of harmonising supply chains, using one product instead of two, for severe and moderate wasting together with reduced RUTF dosage for treatment of severe wasting. These overall health systems implications need to be modelled.

RESEARCH AREA:

4 EFFECTIVE TREATMENT OF DIARRHOEA IN CHILDREN WITH SEVERE ACUTE MALNUTRITION (SAM)

RECAP: OUTSTANDING RESEARCH NEEDS IDENTIFIED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

TREATMENT OF DIARRHOEA IN CHILDREN WITH SAM:

OUTSTANDING NEEDS	TYPE OF EVIDENCE/RESEARCH NEEDED
Improved recognition of the signs of dehydration and monitoring of rehydration process within inpatient treatment	▪ Implementation research to test improvements to the application of existing guidelines and identify further research gaps
Evidence on the pathogenic co-morbidity and risk of mortality in children with diarrhoea	▪ Inclusion into broader research studies currently being planned
Evidence on the effectiveness of nitazoxanide for the treatment of cryptosporidium infections and associated diarrhoea in children with SAM	▪ Systematic review of existing evidence available across completed studies
Review and update of the evidence supporting guidelines for the treatment of chronic diarrhoea	▪ Systematic review of existing evidence available across completed studies

SUMMARY OF RECENTLY EMERGING EVIDENCE

An overview of completed, ongoing, and planned research in this area identified in the Landscape Review can be found [here](#).

There is very limited direct evidence on the management of children with severe wasting and diarrhoea in community settings and studies on managing severe wasting in CMAM programmes with RUTF rarely measure diarrhoea as an outcome. There is increasing evidence that CHWs can detect complications in children with severe wasting, including diarrhoea. Recent reviews of fluid management in severely wasted children found that some studies suggest that global guidelines for oral and IV rehydration may be inappropriate^{11 12}. Ongoing research is further exploring this question. Several recent studies suggest that the frequency of occurrence of a range of pathogens is not different in malnourished and well-nourished children with diarrhoea, including cryptosporidium.

This suggests that more severe diarrhoea in severely wasted children may be due to impaired host response to infection or late presentation rather than higher prevalence of specific pathogens. However, diversity in studies in settings and methods and the fact that more than one pathogen is commonly found in the same child with diarrhoea make it difficult to draw conclusions about pathogens that may occur more often in children with wasting.

PROGRESS TOWARDS 2020 OUTCOMES

RECAP: OUTCOMES BY 2020 DEFINED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

All children with SAM who also experience acute watery or chronic diarrhoea receive safe and effective treatment.

POLICY-LEVEL: Global and national policies and guidance are clear and easily accessible. Where needed, interim guidance is made available for emergency contexts.

OPERATIONAL-LEVEL: Operational guidance on the implementation of global and national policies is clear and easily accessible to inform programmes in both emergency and non-emergency contexts.

11 Houston K, Gibb J, Maitland K. Oral rehydration of malnourished children with diarrhoea and dehydration: A systematic review [version 3; peer review: 2 approved]. Wellcome Open Research. 2017;2(66).

12 Houston K, Gibb J, Maitland K. Intravenous rehydration of malnourished children with acute gastroenteritis and severe dehydration: A systematic review [version 1; peer review: 3 approved]. Wellcome Open Research. 2017;2(65)

Two recent research reviews highlighted that global guidelines on fluid management in children with severe wasting with diarrhoea or dehydration highlighted concerns about current guidelines. The review of oral rehydration of severely wasted children found that evidence from South Asia suggests that the recommended use of ReSoMal may cause harm because hyponatraemia may pose greater risks than hypokalaemia and ReSoMal has been found to result in higher development of hyponatraemia¹³. Current guidelines may underestimate the risks of hyponatraemia. Evidence from South Asia suggests that ReSoMal can be replaced by ORS, but there is no evidence on ORS for rehydration from sub-Saharan African settings. Moreover, more aggressive IV rehydration approaches may be appropriate for severely wasted children with severe dehydration and/or shock: A recent review on IV rehydration for severely wasted children found no published evidence that severely wasted children are more at risk of heart failure when given IV fluids or at risk of fluid overload. More research is needed on the type of oral rehydration, on the route of administration and on the rate. The issue of a more aggressive approach to treatment of diarrhoea in severely wasted children with cholera has been raised by members of the Global Task Force on Cholera Control. Guidelines on management of dehydration in severely wasted children continue to influence national guidelines (for instance, the Government of Ethiopia has recently updated their diarrhoea management guidelines in line with WHO recommendations). There is also little research on community-based management of severe wasting and diarrhoea (with or without dehydration) beyond health facilities.

RECOMMENDATIONS FOR FURTHER RESEARCH

Research on fluid management in severely wasted children

- More research is required on oral rehydration management in severely wasted children, including on what fluids to use in what circumstances and on adequate volumes and routes of administration. Particularly, evidence from sub-Saharan African settings is needed on whether ReSoMal can be replaced by oral rehydration solution (ORS). Research is also required on whether more aggressive IV rehydration approaches are appropriate for severely wasted children with severe dehydration and/or shock as withholding IV fluids may leave children dehydrated.

Operational evidence and guidelines on rehydration in severely wasted children

- There is need for clearer guidance for frontline health workers, particularly for the management of children who are wasted and have diarrhoea outside of hospital settings. Some progress has been made at a policy level with WHO working groups to improve guidance. This includes the development of a job aide by the Global Task Force for Cholera Control, although operational evidence is needed to identify challenges in implementing the job aide.
- Existing and emerging evidence should be summarised in close coordination with national and international bodies to ensure that policy and operational implications of research are recognised. Interim guidance could be produced where appropriate while new evidence is being generated.

Focus on management of diarrhoea in wasted children rather than pathogenic causes

- Recent research suggests that the prevalence of a range of pathogens does not differ between malnourished and well-nourished children with diarrhoea and so far no wasting specific pathogen has been singled out. This includes cryptosporidium. Diversity in terms of settings and methods to identify pathogens and the fact that often a range of pathogens are found in same child so that establishing causality is usually not possible mean that no pathogen specific for wasting can be singled out.
- The identification of pathogens specific to wasting is a lower priority given the mixed evidence and urgent need for evidence on management. Linked to this, research on nitazoxanide as treatment for cryptosporidium is limited and should not be a priority.

13 Houston K, Gibb J, Maitland K. Oral rehydration of malnourished children with diarrhoea and dehydration: A systematic review [version 3; peer review: 2 approved]. Wellcome Open Research. 2017;2(66).

RESEARCH AREA:

5 RATES AND CAUSAL FACTORS OF POST-TREATMENT RELAPSE TO ACUTE MALNUTRITION ACROSS CONTEXTS

RECAP: OUTSTANDING RESEARCH NEEDS IDENTIFIED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

ESTIMATING THE BURDEN AND CAUSAL FACTORS OF RELAPSE:

OUTSTANDING NEEDS	TYPE OF EVIDENCE/RESEARCH NEEDED
Development of a standardised definition of relapse and recommendations for measurement	<ul style="list-style-type: none"> Systematic review/meta-analysis of existing data and evidence available across completed studies.
Estimate of the burden of relapse and, if possible, identify potential risk factors for relapse across different contexts	<ul style="list-style-type: none"> Analysis and modelling using existing data available across completed studies. Inclusion of post-treatment relapse measurement in upcoming research studies.

IF BURDEN OF RELAPSE IS FOUND TO BE HIGH:

OUTSTANDING NEEDS	TYPE OF EVIDENCE/RESEARCH NEEDED
Testing of effective interventions to reduce post-treatment relapse	<ul style="list-style-type: none"> Implementation research
Establish minimum standards for excess relapse and operational guidelines to support programmes in reducing relapse.	<ul style="list-style-type: none"> Systematic review/meta-analysis of existing data and evidence available across completed studies.

SUMMARY OF RECENTLY EMERGING EVIDENCE

An overview of completed, ongoing, and planned research in this area identified in the Landscape Review can be found [here](#).

Two recent systematic reviews summarised the evidence on relapse and long-term outcomes after treatment for severe wasting^{14 15}. The reviews suggested that relapse may be a significant problem, with most relapse occurring between 3-6 months following discharge, but there was variation in definitions and measurement of relapse as well as admission and discharge criteria, making comparisons difficult. There are also few studies that compared rates of relapse with rates of new occurrence of wasting in a control group of children who were not previously malnourished. There is a large body of ongoing research on relapse, including a study in four sub-Saharan African countries that includes a community control group to compare relapse with background incidence of severe wasting¹⁶. The systematic review on post-treatment relapse⁸ found poorer anthropometric measurements at admission and discharge to be most consistently associated with increased risk for relapse. Beyond anthropometric measures, there are fewer studies on causes of relapse and there is a widespread lack of distinction between associations and causality. It is often unclear whether measured factors were present at time of admission or became relevant after discharge. More broadly, there is lack of a theoretical framework for relapse to support harmonisation on this issue.

14 Stobaugh HC, Mayberry A, McGrath M, Bahwere P, Zagre NM, Manary MJ, et al. Relapse after severe acute malnutrition: A systematic literature review and secondary data analysis. *Maternal & Child Nutrition*. 2019;15(2):e12702.

15 O'Sullivan NP, Lelijveld N, Rutishauser-Perera A, Kerac M, James P. Follow-up between 6 and 24 months after discharge from treatment for severe acute malnutrition in children aged 6-59 months: A systematic review. *PLoS One*. 2018;13(8):e0202053.

16 <https://www.actionagainsthunger.org/research/sam-relapse>

PROGRESS TOWARDS 2020 OUTCOMES

RECAP: OUTCOMES BY 2020 DEFINED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

A standard definition of relapse post-treatment is available and consistently measured across research. Estimation of readmission, based on a standard definition and methodology, is also regularly monitored in programmes. The burden of relapse across contexts is clearly understood and, where burden is high, there are effective interventions to prevent it.

POLICY-LEVEL: Global and national policies include a standard definition of relapse post-treatment for acute malnutrition.

OPERATIONAL-LEVEL: Relapse is consistently measured in research projects and programmes and, where burden is high, there are clear minimum standards for relapse and interventions in place to mitigate risk of relapse.

There is no standard definition of post-treatment relapse to moderate or severe wasting and no consistent measurement across research or programme monitoring. The burden of and risk factors for relapse across contexts continue to be poorly understood.

RECOMMENDATIONS FOR FURTHER RESEARCH

Develop a standardised definition of post-treatment relapse and a conceptual framework

- Developing standardised definitions of relapse and regression to and reoccurrence of wasting after receiving treatment is of central importance. A standardised definition is necessary for establishing minimum standards for excess relapse and developing guidance to support programmes in reducing relapse.
- Based on the reviews of the latest evidence, CORTASAM has generated recently published a statement suggesting a standardised definition of relapse, including for research and programmes and called for feedback from researchers and practitioners with the aim to update it as new evidence emerges¹⁷.
- Linked with the recommendations for standardised definitions and measurement of post-treatment relapse, a conceptual framework for relapse after exit from treatment has recently been developed by some members of CORTASAM and the No Wasted Lives Secretariat¹⁸. This framework identifies key pathways and differentiates between causal factors for wasting that were present before treatment and may still be present after treatment and causal factors specific to relapse to wasting. The objective of this framework is to guide development and testing of effective interventions to reduce post-treatment relapse.
- Current ongoing research should be optimised so that the latest guidance on definitions and measurement are reflected and to ensure that critical outstanding questions are addressed.

Frame issues around post-treatment relapse at an operational level

- The problem of relapse to wasting after receiving treatment should, in the short-term, be framed at an operational level, with a definition and framework providing guidance for research and programmes and the importance of context being recognised, rather than aiming for a globally accepted definition and global estimates for relapse.

¹⁷ The Council of Research & Technical Advice for Acute Malnutrition (2020). *Guidance to improve the collecting and reporting of data on relapse in children following treatment in wasting programmes.*

¹⁸ Schaefer R, Mayberry A, Briend A, Manary M, Walker P, Stobaugh H, Hanson K, McGrath M, Black R. Relapse and regression to severe wasting in children under 5 years: A theoretical framework. *Maternal and Child Nutrition.* 2020;e13107.

RESEARCH AREA:**6 IDENTIFICATION AND MANAGEMENT OF NUTRITIONALLY AT-RISK MOTHERS AND INFANTS <6 MONTHS OF AGE (MAMI)****RECAP: OUTSTANDING RESEARCH NEEDS IDENTIFIED IN THE RESEARCH AGENDA**

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

CORTASAM is working with the MAMI SIG (Special Interest Group) to progress the following research priorities:

TREATMENT OF DIARRHOEA IN CHILDREN WITH SAM:**OUTSTANDING NEEDS**

Demonstration of an approach to identify and manage small and nutritionally at-risk infants <6m across contexts to influence country-level policies and roll-out.

TYPE OF EVIDENCE/RESEARCH NEEDED

- Robust trials, with priority to randomised control trials, to explore the effectiveness and cost-effectiveness of MAMI programmes.

- Implementation research across contexts to demonstrate replicability and scalability of the model.

SUMMARY OF RECENTLY EMERGING EVIDENCE

An overview of completed, ongoing, and planned research in this area identified in the Landscape Review can be found [here](#).

PROGRESS TOWARDS 2020 OUTCOMES**RECAP: OUTCOMES BY 2020 DEFINED IN THE RESEARCH AGENDA**

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

Simplified new criteria to identify small and nutritionally at-risk infants, scalable packages of care focusing on outpatient management are being tested across multiple contexts, informed by context-specific burden data.

POLICY-LEVEL: Simplified new criteria for identifying small and nutritionally at-risk infants have been agreed; national policy makers recognise outpatient management of infant with clinically uncomplicated malnutrition as per WHO 2013 SAM guidelines; infants <6m are included in routine anthropometric surveys.

OPERATIONAL-LEVEL: Operational guidance based on best current evidence supports caseload estimation and roll-out of programmes focused on identification and management of small and nutritionally at-risk infants at scale and across contexts.

There has been progress towards the 2020 outcomes at policy and operational levels. Activities by the MAMI Global Network, previously the MAMI SIG¹⁹ have been guided by research priorities identified in a consultative prioritisation in 2015 (top five priorities called for clear case definition, integration into existing health services and tools, efficacy of targeted support on breastfeeding)²⁰. We are closer to consensus on criteria to identify small and nutritionally at-risk infants both through growing evidence that identifies weight-for-age (WAZ) and mid upper arm circumference (MUAC) as good anthropometric markers of risk for this age group, and evolving operational experiences and consultation applying and examining feeding, clinical and maternal indicators as part of a package of maternal and infant care. Low birth weight infants have been highlighted as a particular at risk group of infants.

19 An active international collective of programmers, researchers and policy-makers working to build evidence and impact on relevant practice and policy coordinated by ENN and coOled by ENN and LSHTM. The MAMI SIG will shortly scale into a MAMI Global Network. <https://www.ennonline.net/ourwork/research/mami>

20 Angood C, McGrath M, Mehta S, Mwangome M, Lung'aho M, Roberfroid D, Perry A, Wilkinson C, Israel A-D, Bizouerne C, Haider R, Seal A, Berkley JA, Kerac M. (2015) Research Priorities to Improve the Management of Acute Malnutrition in Infants Aged Less Than Six Months (MAMI). *PLoS Med* 12(4): e1001812. <https://doi.org/10.1371/journal.pmed.1001812>.

At an international policy level, a 2019 consultation by WHO on growth failure in infants under six months galvanised experts and programmers across neonatal, paediatric and nutrition disciplines and development and humanitarian contexts to identify five priority areas of research to inform case management and WHO policy direction²¹. Looking ahead, infants under six months will be explicitly addressed in an update of WHO wasting treatment guidelines (due for release end 2021) that will frame case identification and management of all infants in terms of risk. Infants under six months are explicitly addressed in the UN Global Action Plan on Wasting Framework released in March 2020²². Most recently, WHO/UNICEF implementation guidance on wasting management in the context of COVID-19 includes infants under six months and includes WFA and MUAC as an acceptable programming adaptation to identify at risk infants²³. At national level, a review of country uptake of community based management of infants under six months in national wasting treatment guidelines is being updated and due for publication in late 2020; it reflects that several countries are now accommodating infants under six months in guidelines modelled on the MAMI Tool (India, Afghanistan, Philippines) that reflects positive direction of travel.

In terms of approaches to case management the C-MAMI Tool, developed in 2015 to support management and updated in 2017, has been implemented and piloted in several contexts (Bangladesh, Ethiopia), and is currently being updated by the MAMI SIG into a MAMI care pathway, informed by an experienced working group across specialities (including nutrition, paediatrics, early childhood development, maternal mental health), contexts and stakeholders (including national representation from India and Ethiopia) and will be available for pilot in 2021²⁴. Most recently, the COVID-19 pandemic has heightened the need to intervene early to protect and support infants under six months and their mothers²⁵.

In terms of evidence, through 2019 and 2020, there has been more published research on MAMI including on medical interventions, breastfeeding efficacy and anthropometric indicators of risk. Recently published analyses of longitudinal cohort data spotlights considerable burden of wasting at birth and incident wasting in the early months of life, how this is associated with significantly increased risk of death, subsequent wasting, stunting, and persistent wasting, and calls for prioritisation of pre-natal and early life health and nutrition interventions to prevent and treat wasting^{26 27 28}. A significant and long awaited development in our drive to generate quality evidence is that a randomised controlled trial of the MAMI care pathway that is now in its formative phase, for implementation 2021-2023 in Ethiopia by LSHTM, Jimma University, GOAL and ENN funded by the Eleanor Crook Foundation²⁹. A multi-centre trial of interventions on growth failure in this age group is also in development, implemented by multiple partners funded by the Gates Foundation.

At an operational level, there remains strong and engaged commitment from UN agencies, NGOs and government to address at risk infants under six months³⁰. Dedicated technical assistance on MAMI to countries is available through the Global Nutrition Cluster Technical Alliance, hosted by Save the Children, funded by OFDA and connected to the MAMI Global Network. Reflecting this appetite and potential, the MAMI SIG was scaled up by the ENN into a MAMI Global Network in 2020, to leverage expertise across multiple disciplines and contexts and step up to the ongoing challenges and opportunities on MAMI³¹.

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- 21 WHO (2019). *Research priorities to prevent, identify and manage young infants with growth failure in the first six months of life. Meeting report draft.*
- 22 WHO, FAO, UNHCR, UNICEF, WFP (2020). *Global action plan on child wasting. A framework to accelerate progress in preventing and managing child wasting and the achievement of the sustainable development goal*
- 23 UNICEF & WHO (2020). *Prevention, Early Detection and Treatment of Wasting in Children 0-59 Months through National Health Systems in the Context of COVID-19.*
- 24 <https://www.ennonline.net/ourwork/research/mami>
- 25 Emergency Nutrition Network and Global Technical Assistance Mechanism (2020). *Statement on management of at-risk mothers and infants under six months (MAMI) in the context of COVID-19*
- 26 Mertens A, Benjamin-Chung J, Colford JM, Coyle J, van der Laan M, Hubbard AE et al (2020). *Early childhood linear growth failure in low- and middle-income countries* MedRxiv, The preprint server for Health sciences; doi: <https://doi.org/10.1101/2020.06.09.20127001>
- 27 Mertens A, Benjamin-Chung J, Colford JM, Hubbard AE, van der Laan M, Coyle J, et al (2020). *Child wasting and concurrent stunting in low- and middle-income countries.* MedRxiv, The preprint server for Health sciences; doi: <https://doi.org/10.1101/2020.06.09.20126979>
- 28 Mertens A, Benjamin-Chung J, Colford JM, Coyle J, van der Laan M, Hubbard AE, et al (2020). *Causes and consequences of child growth failure in low- and middle-income countries.* MedRxiv, The preprint server for Health sciences; doi: <https://doi.org/10.1101/2020.06.09.20127100>.
- 29 <https://www.ennonline.net/ourwork/research/mami>
- 30 Emergency Nutrition Network (2019). *Meeting report: Management of At risk Mothers and Infants under six months (MAMI) Special Interest Group (SIG) meeting.*
- 31 *Updates to activities and emerging resources will be made available at: <https://www.ennonline.net/ourwork/research/mami>*

It remains that clear, coordinated, evidence-based global guidance informed by multiple contexts is needed for countries to effect the necessary institutional, policy and system development required to advance case identification and management and inform and drive policy and programming development.

Key areas for future work include the following:

Evidence generation on tools and approaches to identify and manage at-risk infants under six months and mothers across contexts

- Coordinated formal and operational research to increase the strength of evidence on case definition and approaches to identify and manage infants under six months who are small and nutritionally at risk.
- Engagement with and across sectors including health, early childhood development, maternal mental health and neonatal health.
- Cross-context evidence and experience generation that must include South Asia

Support to uptake of guidance and approaches

- Active dissemination of key resources through global and regional networks.
- Engagement in WHO guideline development process and with national and international policy-makers
- Commitment to active learning.
- Support regional and country level advocacy and action.



7 RESEARCH AREA: ALTERNATIVE FORMULATIONS FOR READY-TO-USE FOODS FOR ACUTE MALNUTRITION

RECAP: OUTSTANDING RESEARCH NEEDS IDENTIFIED IN THE RESEARCH AGENDA

This box lists the outstanding research needs as identified in the Research Agenda for Acute Malnutrition published in 2018.

“For research area seven the Council is calling for a continuation of the large amount of ongoing research to investigate the effectiveness, and cost-effectiveness, of formulas using alternative and local ingredients. Therefore, there is no call for additional new research in this document.”

SUMMARY OF RECENTLY EMERGING EVIDENCE

An overview of completed, ongoing, and planned research in this area identified in the Landscape Review can be found [here](#).

There are many different types of alternative formulations of RUTF. Most commonly, these aim at replacing or reducing milk and/or peanut content of standard RUTF. Several of these formulations are non-inferior in terms of recovery from severe wasting, but most tested in a small number of RCTs offer no additional clinical benefits. Further research has focused on changing the fatty acid profile of RUTF, with one study suggesting that a RUTF formulation with high oleic peanuts may increase docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) levels among children receiving treatment³². Few studies suggest benefits of pre- and probiotics but there is limited research on this topic. Some research suggests that emulsifiers in standard RUTF formulations may be harmful. Most studies have been conducted in sub-Saharan Africa (particularly Malawi). No studies were found that have considered the wider economic implications of alternative formulations (e.g. in terms of using local products and producing locally). Studies on acceptability found similar or higher acceptability of alternative formulations compared to the standard RUTF formulation.

RECOMMENDATIONS FOR FURTHER RESEARCH

Differentiate between types of alternative formulations of RUTF

- Different types of alternative formulations of RUTF with different modifications to standard RUTF formulations (e.g. milk/peanut-free RUTF, increased omega-3 content, etc.) should not be grouped together. Meta-analyses of all alternative formulations vs. standard RUTF are not helpful and limit the conclusions that can be made for specific modifications to formulation. Specific reviews (rather than reviews of all alternative formulations) could be more helpful to guide discussions and review processes. A systematic review on safety and effectiveness of RUTF with reduced milk protein content, coordinated by WHO, has been conducted (in press) to inform a new guideline on dairy protein content in RUTF (underway). Research gaps identified by WHO in this process should be prioritised. Further reviews could focus on 1) sucrose content, 2) cereal types and content, and 3) other modifications.
- Differentiating between different types of alternative formulations can support identifying research needs. Several trials have been conducted on the three types of alternative formulations mentioned above, so new trials may not be a priority.
- Given the breadth of efficacy studies that have been implemented at small-scale and in highly controlled settings, new trials on alternative formulations should test effectiveness of products in home-based settings at operational scale, with a minimum level of non-inferiority to standard products.

Evaluate effects of emulsifiers in RUTF formulations

- Current mainstream formulations of RUTF include emulsifiers to reduce visible separation of oil, but benefits of emulsifiers are largely cosmetic and not listed under WHO requirements. Given indications that addition of emulsifiers may be harmful, research on alternative formulations without emulsifiers is required to test for efficacy, acceptability, effectiveness, and operational feasibility. A review, looking more broadly at the addition of emulsifiers into other infant and child products, could be of value.

Evaluate secondary outcomes and wider economic and health system implications of alternative RUTF formulations

- Costs, cost-effectiveness, and acceptability are important considerations when considering alternative formulations. These should be evaluated to complement studies on efficacy and effectiveness.
- Body composition, long-term growth, and neurocognitive outcomes should be evaluated. Neurocognitive outcomes are relevant for studies on alternative fatty acid profile formulations.
- Particularly when evaluating body composition and long-term outcomes, attention should be paid to amounts and types of amino acids provided. Coordination with WHO-convened committee on RUTF protein sources is necessary.
- Even if costs per RUTF dose are similar between alternative formulations and standard RUTF, alternative formulations can have wider economic implications, e.g. in terms of using local products and producing locally. There are also health system implications through effects on supply chains. These wider implications for local economies and health systems need to be evaluated as they could represent a key advantage of alternative formulations. Modelling studies could support this.
- Another wider implication could be lower carbon emissions from local production and reducing transport emissions as well as removing dairy products from RUTF.
- Define more standardised consistent approaches to examining costs, cost-effectiveness and the economies of supply source and management to enable comparisons across different formulations.
- Examine the role of the private sector in the development and delivery of RUTF formulations.

Alternative formulations of RUTF for the combined management of moderate and severe wasting

- Given increasing interest in combined management of moderate and severe wasting, alternative formulations could be explored in this area. Research is needed on the effectiveness of alternative formulations for management of moderate wasting and whether the same product can be used for managing severe and moderate wasting.

Alternative vs. complementary formulations of RUTF

- Alternative formulations could not just replace standard RUTF but also complement management of severe wasting. For instance, after an initial recovery phase using standard RUTF, an alternative RUTF formulation could be used until full recovery from severe wasting. However, there is limited research on this given that there is a general focus on replacing standard RUTF.