Systematic Review Protocol

REVIEWER CONTACT DETAILS:

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REVIEW TEAM

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Title of review:

Resource use, cost and cost-effectiveness of decisions on the setting of treatment initiation, referral, transfer and discharge of infants and children with moderate/ severe wasting and oedema, and infants with growth failure/ faltering: a systematic review

Ethics declaration:

This study will use secondary, anonymised data. Ethics approvals are deemed not applicable.

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1. BACKGROUND

Child wasting refers to a child who is too thin for their height.[1,2] It is the result of recent rapid weight loss or the failure to gain weight and can develop rapidly in the face of poor nutrient intake and/or disease.[1] In 2020, an estimated 45.4 million children, i.e., ~6.7% of the world's children, who are under 5 years of age, were affected by wasting, of which 13.6 million were severely wasted.[1] The highest prevalence of wasting is in low- and middle-income countries (LMICs), with the majority of cases being in Sub-Saharan Africa and South Asia.[3] For some LMIC contexts, this has been attributed to many factors, including poverty, adverse climatic conditions, policies, corruption, social, cultural and religious factors.[4]

A moderately or severely wasted child requires urgent treatment: they have weakened immunity, are susceptible to long-term developmental delays, and have a 5- to 20-fold increased risk of death.[2,3,5] Globally, each year, about 4.4% of deaths among children under the age of 5years are attributable to severe wasting.[4] In 2013, the World Health Organisation (WHO) published guidelines for severe acute malnutrition (severe wasting and oedema).[2] These guidelines have several gaps, including in the following areas: recommendations for infants under six months of age, the management of moderate wasting, and economic evidence to support decision making. WHO is currently developing guidelines for prevention and treatment of wasting, which will include four overlapping areas of focus, i.e.: 1) growth faltering/failure in infants younger than six months; 2) moderate wasting in infants and children aged six months and older; 3) severe wasting and oedema in infants and children aged six months and older; and 4) prevention of wasting.

Research on child wasting has focused on the health and human impacts of child undernutrition,[6] leaving an evidence gap on the economic impacts, including the resource requirements, costs and cost-effectiveness of decisions on the setting of treatment initiation, referral, transfer and discharge of children $\leq$5years of age with child wasting. We identified two relevant systematic reviews on resource use, costs and cost-effectiveness; one aimed to estimate the costs and cost-effectiveness of child undernutrition treatment(s) to households, health providers, organizations and governments in LMICs.[6] The other focused on cost-efficiency and cost-effectiveness of programmes that treated severe acute malnutrition (SAM) at the community level

(in outpatient facilities or by community health workers), with or without additional management of moderate acute malnutrition (MAM).[7] Whilst these two reviews provide valuable information to policymakers, they do not provide information that could be used to drive decisions on the setting of treatment initiation, referral pathways, and transfer and discharge strategies. Thus, our systematic review complements these reviews by focusing on economic evidence on resource use, cost and cost-effectiveness of decisions on the setting of treatment initiation, referral, transfer and discharge of: 1) infants younger than six months of age with growth faltering/failure; and 2) infants and children aged from six months to 5 years with moderate wasting, severe wasting and oedema.

2. REVIEW QUESTIONS

The systematic review seeks to address the following questions for infants younger than six months of age with growth faltering/failure; and infants and children aged from six months to 5 years with moderate wasting, severe wasting and oedema:

1. What resources are required for:
    a. initiation of treatment in a community setting,
    b. initiation of treatment in outpatient settings,
    c. Referral to treatment from community to outpatient settings,
    d. referral to treatment in an inpatient setting,
    e. transfer from inpatient to outpatient/community treatment,
    f. transfer from outpatient to community settings,
    g. discharge from outpatient/community treatment?
2. What are the costs associated with:
    a. initiation of treatment in a community setting,
    b. initiation of treatment in outpatient settings,
    c. Referral to treatment from community to outpatient settings,
    d. referral to treatment in an inpatient setting,
    e. transfer from inpatient to outpatient/community treatment,
    f. transfer from outpatient to community settings,
    g. discharge from outpatient/community treatment?
3. What is the cost-effectiveness of:
    a. initiation of treatment in a community setting,

b. initiation of treatment in outpatient settings,
c. Referral to treatment from community to outpatient settings,
d. referral to treatment in an inpatient setting,
e. transfer from inpatient to outpatient/community treatment,
f. transfer from outpatient to community settings,
g. discharge from outpatient/community treatment?

4. What is the certainty of this evidence identified in 1, 2 and 3 above?

3. METHODS

The approach will mainly comprise a systematic review guided by well-established standardised principles and methods, including a pre-written protocol.[8,9]

3.1. Inclusion/ exclusion criteria

Our initial scoping searches have revealed that most studies on child wasting report the results for infants and children up to 59 months (or <5 years) of age without subgroup analyses for those aged 6 to 59 months. Similarly, for growth failure/faltering in infants, studies report results for <12 months without subgroup analyses for those <6 months. In order not to lose important and potentially applicable evidence, we will include studies on moderate wasting and/or severe wasting and/or bilateral pitting oedema in children aged <5 years; and studies on growth failure/faltering in infants <12 months. When reporting the results, we will distinguish between evidence coming from 6 to 59 months versus 0 to 59 months studies; or <6 months versus <12 months studies. The inclusion/ exclusion criteria has been defined using the Population(s), Intervention(s), Comparator(s), Outcome(s), Study design(s) (PICOS) framework (Table 1).[8,9]

Table 1: Inclusion/ Exclusion criteria

Selection Criteria	**Inclusion**	**Exclusion**
Population	Infants and children <5 years of age with moderate wasting or severe wasting and/or bilateral pitting oedema. Infants <12 months of age with growth failure/ faltering	For moderate and severe wasting and/or oedema Other children ≥5 years of age with moderate wasting or severe wasting and/or bilateral pitting oedema. Infants and children <5 years of age who do not have moderate wasting or severe wasting and/or bilateral pitting oedema. Mixed populations that include the population of interest (i.e., infants and children <5 years of age with moderate or severe wasting and/or oedema) but where data for the population of interest is not reported separately. For growth failure/ faltering: Infants and children ≥12 months of age with growth faltering or failure Infants <12 months of age who do not have growth failure or faltering.

Selection Criteria	**Inclusion**	**Exclusion**
		Mixed populations that include the population of interest (i.e., infants <12 months of age with growth failure/ faltering), but where data for the population of interest is not reported separately.
Intervention	For wasting or growth failure/faltering: • initiation of treatment in a community setting. • initiation of treatment in outpatient settings. • referral to treatment in an inpatient setting. • transfer from inpatient to outpatient/community treatment • discharge from outpatient/community treatment. •	Other interventions that are not those listed in the inclusion criteria.
Comparators	Not restricted (with or without a comparator)	N/A

Selection Criteria	**Inclusion**	**Exclusion**
Outcomes	Resource use Costs Cost-effectiveness estimates based on a) cost outcome analysis (e.g., cost per child seen etc.), or b) full cost-effectiveness analysis (e.g., cost per life years saved etc.).	• Not reporting the outcomes of interest. • Only indirect costs reported, such as productivity loss. • Only including costs of medicinal food with no setting-related costs
Study type	Any type of economic analysis (including cost and cost-effectiveness or cost-utility analyses) reporting cost estimates based on a) patient-level data, b) expenditure or c) ingredients, or a combination thereof, or calculating costs based on treatment pathways in clinical guidelines	Systematic reviews and other types of literature reviews to avoid double counting
Language	No restrictions	N/A
Other	Studies that are available online	Studies where the full text is not available (e.g., only published as an abstract)

Selection Criteria	**Inclusion**	**Exclusion**
		Publications which do not report relevant outcomes (e.g., study protocols, commentaries and letters for the Editor)

3.2. Search Strategy

We will follow Cochrane MECIR and CRD guidelines in designing, PRESS in peer-reviewing, and PRISMA-Search for reporting the search. An information scientist will design the search strategies in collaboration with the expert review team.

3.2.1. Search terms

The search terms were selected from experts' opinions, literature review, reviewing the results of scoping searches, and controlled vocabularies (Medical Subject Heading=MeSH, Excerpta Medica Tree=Emtree, and EconLit Thesaurus). The terms will be arranged into three blocks, as exemplified below for one of the electronic databases.

MEDLINE via Ovid SP

Database: Ovid MEDLINE(R) ALL <1946 to December 10, 2021>

1 (exp Child/ or exp Infant/ or Infant, Newborn, Diseases/ or (Child or Children or Childhood or Pre-school or Pre-schools or Preschool or Preschools or Infant or Infants or Infantile or New-Born or New-Borns or Newborn or Newborns or Neonate or Neonates or Neonatal or Toddler or Toddlers or Baby or Babies or "Early Life").ti,ab.)

and

2 (Wasting Syndrome/ or Failure to Thrive/ or Growth Disorders/ or Malnutrition/ or Child Nutrition Disorders/ or Infant Nutrition Disorders/ or exp Severe Acute Malnutrition/ or Starvation/ or Edema/ or Hydrops Fetalis/ or exp Protein Deficiency/ or Fetal Growth Retardation/ or (Waste or Wasted or Wasting or Stunt or Stunted or Stunting or Under Nutrition or UnderNutrition or Malnutrition or Under Nourished or Under Nourishment or Malnourished or Malnourishment or "Low Weight-For-Height" or "Low WFH" or "Severe Weight Loss" or "Rapid Weight Loss" or "Under Fed" or "Under Feed" or "Under Feeding" or Underfeeding or Underfed or Underfeed or "Under Weight" or Underweight or "Low Weight-For-Age" or "Low WFA" or "Low Birth Weight" or "Low Birthweight" or "Small for Gestational Age" or "Small

for Date" or "Small for Age" or "Failure to Thrive" or "Growth Failure" or "Growth Faltering" or "Growth Disorder" or "Growth Disorders" or "Low Weight For Length" or "Low Mid Upper Arm Circumference" or Kwashiorkor or Marasmus or Starved or Starvation or Starving or Oedema or Oedemas or Oedematous or Edema or Edemas or Edematous or Hydrops or Dropsy or Anasarca or "Protein Deficiency" or "Protein Deprivation" or Prematur* or Pre-Matur* or Preterm or Pre-Term or "Fetal Growth Disorder" or "Fetal Growth Restriction" or "Fetal Growth Retardation" or "Fetus Growth Disorder" or "Fetus Growth Retardation" or "Foetal Growth Disorder" or "Foetal Growth Restriction" or "Foetal Growth Retardation" or "Foetus Growth Disorder" or "Foetus Growth Retardation" or "Growth Retardation in Utero" or "in Utero Growth Restriction" or "in Utero Growth Retardation" or "Intrauterine Growth Restriction" or "intrauterine Growth Restriction" or "Intra-Uterine Growth Restriction" or "Intrauterine Growth Retardation" or "intra-Uterine Growth Retardation" or IUGR or "Prenatal Growth Retardation" or "Retarded Intrauterine Growth").ti,ab.)

and

3 ("Costs and Cost Analysis"/ or Cost-Benefit Analysis/ or exp Cost Control/ or Health Resources/ or exp Resource Allocation/ or exp Health Services Accessibility/ or exp Health Care Costs/ or Health Expenditures/ or exp Economics, Medical/ or (Cost or Costs or Cost-Effective or CostEffective or Cost-Effectiveness or CostEffectiveness or Cost-Efficiency or CostEfficiency or Cost-Efficient or CostEfficient or Cost Benefit or CostBenefit or Cost Benefitial or CostBenefitial or Cost Utility or CostUtility or "Cost Analysis" or Affordability or "Economic Evaluation" or "Economic Evaluations" or "Econometric Analysis" or "Economic Benefit" or "Economic Benefits" or "Marginal Analysis" or "Resource Allocation" or "Resources Allocation" or "Allocation of Resource" or "Allocation of Resources" or "Allocative Efficiency" or "Health Care Rationing" or "Healthcare Rationing" or Finance or Finances or Financial or Financed or Expense or Expenses or Budget or Budgets or Budgeting or Expenditure or Expenditures or "Health Care Access" or "Health Care Accessibility" or "Access to Health Care" or

"Healthcare Access" or "Healthcare Accessibility" or "Access to Healthcare").ti,ab.)

3.2.2. Sources to be searched

Study sources are:

- Center for the Evaluation of Value and Risk in Health (until search date)
- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library (until search date)
- Cochrane Database of Systematic Reviews (CDSR) via Cochrane Library (until search date)
- CRD's NHS Economic Evaluation Database (NHS EED) (available only until 2015)
- CRD's HTA Database (available only until 2015)
- EconLit via ProQuest Dialog (1886 – search date)
- Embase via Ovid SP (1974 – 2021 Week 37)
- Epistemonikos (until search date)
- Google Scholar (including Grey Literature) (until search date)
- INAHTA HTA Database (until search date)
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to search date
- The Global Health Cost-Effectiveness Analysis (GH CEA) Registry (until search date)
- Websites: Action Against Hunger, MSF, Save the Children, UNICEF, WHO, and World Bank (until search date)

3.2.3. Search Limits

No date, study design, publication type, geographic or language limits will be imposed on the searches.

3.3. Study Selection

The Rayyan software (Rayyan – Intelligent Systematic Review) will be used to manage the articles retrieved from the searches. Each article will be independently screened for eligibility by two reviewers using a study screening form based on

prespecified inclusion/ exclusion criteria. The screening form will be piloted to ensure the inclusion criteria can be reliably interpreted and used to appropriately classify studies.[8,9] Disagreements between reviewers will be resolved by referral to a third reviewer.

Titles and abstracts will be screened during the first stage of study selection. Studies that are judged to be potentially eligible from, or for which there was inadequate information to make inclusion decisions during, the first stage will have their full texts screened in the second stage.

3.4. Quality assessment strategy

The methodological or reporting quality of included studies will be assessed using an adaptation of the ISPOR Consolidated Health Economics Evaluation Reporting Standards (CHEERS)- a 24-item checklist, which consists of the minimum set of items that are important to include when reporting economic evaluations.[10] Some of the studies included in the review will not be economic evaluations by definition and as such, some of the items in the checklist will not be applicable. A scoring system will be added to the checklist to grade the quality of each item in the checklist for each study as follows: 0 (not considered), 1 (partially considered), 2 (fully considered) and N/A (where an item on the checklist is not relevant to the study). The item scores will subsequently be summed up and a percentage calculated based on the maximum attainable score. Studies with a percentage score less than 50% will be categorised as low, those with a score between 50% and 74% will be rated as moderate and those with a score of 75% or higher will be categorised as good. For each item on the checklist, the total number of articles reporting it will then be summed up and reported as a percentage of the total number of included articles where that item is applicable. Two reviewers will assess the quality of the included studies independently, with disagreements being resolved by consensus.

We will use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system and the UK National Institute for Health and Care Excellence's economic profiles approach to classify the certainty in the evidence across all studies as very low, low, moderate, and high.[11-13] We will build economic profiles for the evidence for each group/subgroup based on the following: resource

allocation, cost-effectiveness evidence, overall quality of evidence, applicability, certainty and any other limitations (Table 2). Cost-effectiveness analysis will be considered as high quality. For each model of care, if there are serious concerns for at least one of the criteria, the evidence will be downgraded one level (-1), e.g., from high to moderate.[11] The downgrade will be by two levels (-2; e.g., from high to low) if there are very serious concern for at least one of the criteria. Cost analysis wil be considered as low quality, with upgrades (i.e., +1 or +2) for large effect, dose-response, or no confounding.

Table 2: Economic profiles criteria

Criteria	Considerations	Rationale for judgement
Resource allocation	• number of studies reporting the costs of an intervention • how the costs compare with other models of care	• the higher the costs of one model of care compared to the alternatives, the lower the likelihood that a strong recommendation was warranted.[11] • The higher the number of studies reporting consistent results, the higher the likelihood of a strong recommendation.
Cost-effectiveness evidence	• number of studies reporting the costs of an intervention and the incremental cost-effectiveness ratio when compared with other models of care against the appropriate threshold	• if an intervention is cost-effective compared to the alternatives, a strong recommendation is warranted. • The higher the number of studies reporting consistent results, the higher the likelihood of a strong recommendation.
Overall quality of evidence	Based on the CHEERS checklist	• The higher the quality of the evidence, the higher the

Criteria	Considerations	Rationale for judgement
		likelihood that a strong recommendation is warranted.[11]
Applicability	How well does the included evidence answer the review question?[12] • Are the study populations and the interventions being evaluated the same as those depicted in the review question? • Are the comparisons being made between real-life/ viable alternatives?[13]	• Directly applicable if the studies meet all applicability criteria or fail to meet one or more applicability criteria, but this is unlikely to change the conclusions about cost-effectiveness • partially applicable if the studies fail to meet one or more of the applicability criteria, and this could change the conclusions about cost-effectiveness • not applicable if the studies fail to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost-effectiveness.
Certainty	The extent to which there was confidence that an estimate of an effect from the whole body of evidence was adequate to make a decision or a recommendation?[13]	
Other limitations	Other limitations either identified in the study report itself, or by the reviewers.	What are the implications on the confidence in the estimates?

The GRADE definitions will be used where the quality of the evidence is considered as:[11]

- high if there is strong confidence that the true value lies close to the estimated value,
- moderate if the true value is likely to be close to the estimated value, but there is a possibility that it is substantially different,
- low if the true value could be substantially different from the estimated value,
- very low if the true value is likely to be substantially different from the estimated value.

3.5. Data Extraction

Two reviewers will independently extract the relevant data from the included studies using data extraction tables in Microsoft Excel that will be piloted before use and adjusted to ensure it collects all and only relevant data.[9] The data extraction tables will be accompanied by instructions and decision rules for coding data in order to increase consistency, reduce bias from subjective judgement and improve the validity and reliability of the process.[8,9] Disagreements between reviewers will be resolved through discussion and consensus. A third reviewer will be involved should the discussion not bring resolution.

Data extracted will include the categories and variables in Table 3 below:

Table 3: Data extraction categories and variables

Category	Variables
General information	Author Publication year Country Region
Key study methodology characteristics	Study design e.g., trial-based, microsimulation model Type of economic evaluation e.g., cost, CEA, CUA, BIA Comparators Cost perspective Analytical approach (i.e., cost data collection method) Costing period Cost year (reference year for costs) Cost currency Exchange rate Sample size/number of patients Form of child wasting (moderate or severe and oedema)
Targeted population	Age range Gender Ethnicity
Intervention	Type of care i.e., treatment initiation; referral; transfer; discharge Care setting i.e., community, outpatient, inpatient etc.
Outcomes	Type of resources (e.g., staff, capital, equipment, overheads, drugs, transport, hospitalization, other) Cost categories (e.g., direct medical costs, direct non-medical costs, indirect costs, total costs, and cost drivers). Results of cost analysis (cost per?, cost, type of range, low range, high range)

3.6. Data synthesis

Data synthesis will involve a narrative synthesis to generate cost and cost-effectiveness estimated, uncertainty associated with the estimates or any recommendations and the quality of the studies.

Where appropriate, some quantitative outcomes such as costs will be summarised descriptively using means, medians and ranges of the direct and indirect costs according to the perspectives adopted by the included studies. This descriptive analysis will be conducted using STATA version 16. All costs will be converted to US dollars using purchasing power parities (PPPs) for the relevant data year.[14] PPPs, unlike general exchange rates, account for variations between countries in the costs of goods and services.[15] Where appropriate, we will use inflation indices such as consumer price indices to convert costs to 2021 US dollar prices.

Data will be analysed in the following groups:

- Management of growth failure/faltering in infants
- Management of moderate wasting
- Management of severe wasting and/or bilateral pitting oedema
- Management of moderate wasting and severe wasting and/or bilateral pitting oedema together

Within these groups, analysis will be within sub-groups according to the type of management and setting (e.g., initiation of treatment in a community setting, initiation of treatment in outpatient settings, etc.). When reporting our results within these subgroups, we will distinguish between studies of children 6 to 59 months versus 0 to 59 months; or studies of infants <6 months versus <12 months.

Resource use and cost data are highly sensitive to variability in setting, study design and methods and other practical challenges.[16,17] This limits the generalisability and transferability of cost and resource use (and therefore cost-effectiveness) estimates across settings. As such, a meta-analysis of measures of resource use and costs from different studies is generally not robust, and will not generate any meaningful results.[16,17] As such, pooled estimates will only be presented if there is evidence of

little variation in resource use or costs between included studies. This will be done after conversion to a common currency or cost year. The distribution of costs will also be presented.

4. REVIEW TIMELINES

Task	**Completion date**
Focus question	08 September 2021
Draft protocol	20 September 2021
Scoping search	26 November 2021
Final protocol	12 December 2021
Full searches	
Order papers	
Study selection	
Quality assessment	
Data extraction	
Data synthesis	
Draft review submission	
Final review submission	

5. REFERENCES

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