Admission and discharge criteria for the management of severe acute malnutrition in infants aged under 6 months

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Executive summary

Background
Severe acute malnutrition (SAM) is a major global public health problem responsible for over one million young child deaths each year. Most focus to date has been on the management of SAM in children aged from 6 to under 60 months. Recent reports have shown that SAM is also a problem among infants aged under 6 months. Of 20 million children under 5 years with SAM worldwide, 3.8 million are infants. There is a clear need to address and optimize their treatment. This review aims to explore the evidence base underlying current admission and discharge criteria for infants aged under 6 months in SAM treatment programmes.

Methods
We carried out:

1. An Appraisal of Guidelines for Research and Evaluation (AGREE) of national SAM guidelines to determine what various countries were currently recommending in terms of infants aged under 6 months old (0–5.9 months) (infants <6m) SAM treatment, admission and discharge criteria. AGREE is an international, standardized appraisal instrument to assess clinical management guidelines.

2. A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review of published literature to answer the following:

- Can infants <6m with SAM be treated safely and effectively in community settings?
- For infants <6m with SAM, what is the value (indications, effectiveness and safety) of treatment at a variety of admission criteria for supplemental feeding or a dietary intervention, compared to education and counselling alone?
- Which discharge criteria are used to determine the optimal time to conclude feeding/dietary interventions for infants <6m?

Results
AGREE appraisal of national SAM guidelines
Of 36 national SAM guidelines that were reviewed:

- 29 (81%) had specific sections focusing on infant <6m SAM; total page space of guidelines devoted to infants <6m ranged from 1% to 19%, mean 6%;
- all 29/29 guidelines recommended inpatient treatment – one distinguished between clinically complicated and uncomplicated SAM, as they do for older children;
- all 29/29 guidelines recommended supplementary suckling (SS) as the core treatment, the aim being to re-establish effective exclusive breastfeeding (EBF).

Admission criteria for infant <6m SAM consisted of:

- anthropometric criteria that were the same as those for older children in terms of low weight-for-length (W/L) – most commonly, weight-for-length <-3 z-score (WLZ) World Health Organization Child Growth Standards (WHO-GS) was used – but differed in that there was no mid-upper arm circumference (MUAC)-based definition in this age group;
- clinical criteria applied independently of W/L: most commonly if an infant was too weak or feeble to suckle and/or was not gaining weight at home.

Discharge criteria:

- breastfed infants should be gaining weight on breastfeeding alone;
- non-breastfed infants mirrored discharge criteria for older children: reaching a target weight (e.g. 15–20% gain on admission weight or >-1 or >-1.5 z-scores) (WHO-GS).

As a group, the guidelines had many strengths: (i) clearly articulated scope and purpose (AGREE Domain 1); (ii) good professional stakeholder involvement (Domain 2); (iii) good clarity and presentation (Domain 4); and (iv) good tools to support applicability (Domain 5). Major weaknesses were: (i) lack of patient involvement; (ii) poor (or at least poorly expressed) rigour of development (Domain 3); and (iii) lack of clear editorial independence (Domain 6).

GRADE review

High-quality evidence for all of the key study questions was lacking, however, this presents both:

- a weakness since by implication, all current guidelines are based on low-quality evidence;
- an opportunity –since, by implication, there is equipoise and uncertainty around current recommendations; this creates great scope for research and future improvements.

Discussion and recommendations

The evidence base for admission and discharge of infants <6m to treatment programmes is currently weak. There is, however, widespread consensus in national protocols around the following:

- the same anthropometric admission criteria used for child SAM should also apply to infants <6m (most commonly, WLZ <-3); however, MUAC-based admission criteria are not currently cited for infants <6m;
- anthropometry-independent clinical admission criteria are also relevant, e.g. being too weak or too feeble to suckle effectively; mother not having enough milk and infant losing weight.

While there is no evidence directly challenging these guidelines, it is important to note that there are strong arguments for modification of existing guidelines:

- with new WHO-GS, the number of infants <6m below the weight-for-height <-3 z-scores (WHZ) threshold will increase markedly; this risks overwhelming treatment programme capacity and also risks inappropriate interruption of EBF in clinically well but small infants;
- the current inpatient-only model of care for infant <6m SAM is becoming increasingly outdated and discordant with the public-health impact focus of Community Management of Acute Malnutrition (CMAM) for older children.

Studies are urgently needed to explore:

- Clinical and feeding criteria to distinguish clinically *complicated infant <6m SAM* (needing admission to inpatient care) from *uncomplicated infant <6m SAM* (which could potentially be treated in the outpatient/community setting).
- Criteria would have to be appropriately sensitive and specific and would, for example, consider adequacy of breastfeeding, troubleshooting of particular problems with breastfeeding, underlying disease in the infant *and* mother (e.g tuberculosis, HIV) and underlying disability in the infant *and* mother (e.g. maternal depression; mental health problems).
- Community-based treatment for clinically uncomplicated infant <6m SAM – adapted admission/discharge tools with appropriate sensitivity and specificity are needed for this.
- MUAC-based criteria for infants: given its association with muscle and fat mass; to better harmonize with CMAM strategies for older children, enabling active community case finding.

Wherever possible, intervention studies giving high-quality evidence should be done. While awaiting the results from such studies, existing studies and field programmes should be urged to report infant <6m data as a discrete group rather than merged with others. This would facilitate clinical audit and would help shape better intervention research questions.

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Conflicts of interest

None to declare.

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
CI	confidence interval
CMAM	Community Management of Acute Malnutrition
EBF	exclusive breastfeeding
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency syndrome
infant <6m	infant aged under 6 months old (0–5.9 months)
LMIC	low- and middle-income country
MAMI	Management of Acute Malnutrition in Infants
MMI	maternal milk insufficiency
MUAC	mid-upper arm circumference
NCHS	National Center for Health Statistics
NGO	nongovernmental organization
PICO	Population, Intervention, Comparator and Outcomes
RCT	randomized controlled trial
RUTF	ready-to-use therapeutic food
SAM	severe acute malnutrition
SS	supplementary suckling
UN	United Nations
UNICEF	United Nations Children's Fund
W/A	weight-for-age
WAZ	weight-for-age z-score
W/H	weight-for-height
WHO	World Health Organization
WHO-GS	World Health Organization Child Growth Standards
WHZ	weight-for-height z-score
W/L	weight-for-length
WLM	weight-for-length % of median
WLZ	weight-for-length z-score

Measurements

cm	centimetre
g	gram
kg	kilogram
mm	millimetre
n	number

1. Background

Severe acute malnutrition (SAM) is a major global public health problem responsible for over one million young child deaths each year (*1*). Over the last 10 years, significant progress has been made improving the management of SAM and scaling up treatment programmes internationally. Efforts have largely focused on children aged over 6 months, whose treatment has been revolutionized through the development of Community Management of Acute Malnutrition (CMAM) using ready-to-use therapeutic foods (RUTFs) (*2*,*3*). In contrast to this success, acute malnutrition among infants aged under 6 months old (0–5.9 months) (infants <6m) remains inpatient-based and has often been neglected in terms of directed research. This was recently highlighted by the Management of Acute Malnutrition in Infants (MAMI) project (*4*), a multiagency review of current evidence, policy, practice and programme outcomes for SAM infants <6m. Several reasons were identified for the lack of attention to date:

- A common assumption that malnutrition is uncommon in this age group.
  Because infants <6m have a target diet of exclusive breastfeeding (EBF), and because EBF provides optimal nutrition and protects against infections that can precipitate malnutrition, a false logic concludes that infants <6m are, therefore, rarely malnourished. Such a line of reasoning ignores the fact that worldwide rates of EBF are strikingly low: only 25–31% among 2–5 months olds (*5*). It also ignores data: a recent analysis estimated that 3.8 million infants <6m worldwide have SAM as defined by weight-for-height <-3 z-scores (WHZ) World Health Organization Child Growth Standards (WHO-GS) (*6*).

- Treatment of infant <6m SAM is challenging.
  Infants <6m are traditionally not considered eligible for RUTF. Their treatment, aimed at restoring effective EBF whenever possible, requires specialist staff and is time intensive. Neither of these resources is abundant in the resource poor settings where SAM is most prevalent. As a result, services are overburdened and treatment is often reactive (beginning when carers present their infant for treatment) rather than proactive (when health professionals initiate treatment though active case-finding in the community).

- The evidence base underlying current treatments for infant <6m SAM is sparse.

To better manage infants <6m, it is important to improve the evidence base on treatment programme admission and discharge criteria. A systematic review of published studies is currently lacking. This review seeks to fill that gap.

2. Aim

To inform future guidelines on infants <6m SAM by synthesizing current evidence about treatment programme admission and discharge criteria.

2.1 Review questions

- What are country guidelines on SAM currently recommending as admission/discharge criteria for infants <6m?
- Is outpatient (rather than inpatient) care safe and effective for uncomplicated infant <6m SAM?
- For severely malnourished infants <6m, what is the value (indications, effectiveness and safety) of treatment at a variety of admission criteria for supplemental feeding or a dietary intervention, compared to education and counselling alone?
- Which discharge criteria have been used to determine the optimal time to conclude feeding/dietary interventions for infants <6m?

3. Methods

This report comprises two distinct sections: a review of what national SAM treatment guidelines are currently recommending regarding infants <6m; and a review of published literature on current admission/discharge criteria for this age group and associated outcomes using these criteria. We used this two-step approach since we felt it unlikely that published literature would yield sufficient high-quality evidence for us to make strong recommendations about which admission and discharge criteria *should* be used. In this situation, it is important to understand which admission and discharge criteria *are* currently being recommended.

3.1 AGREE review of national guidelines

We reviewed available national guidelines on the management of SAM and extracted data on admission and discharge criteria for infants <6m SAM. We used the Appraisal of Guidelines for Research and Evaluation (AGREE) guideline appraisal tool (http://www.agreecollaboration.org/pdf/aitraining.pdf) as a framework to rate the content and quality of the guidelines. This rates guidelines on a four-point Likert scale where 1=poorest and 4=best. There are six AGREE Domains covering a total of 23 items.

3.2 GRADE review of published literature

We used Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria (www.GradeWorkingGroup.org) to evaluate published literature on infant <6m SAM. This considers a number of different criteria in order to assess study methodological quality: type of study (observational vs randomized); relevant choice of study population; appropriate choice of interventions and outcomes; and methods for controlling for confounders. Subjectivity arising from possible conflicts of interest is also assessed.

3.2.1 Searches

We systematically searched online databases to identify published studies from 1950 to 2011 on the treatment of infant <6m SAM. Databases included PUBMED, Google Scholar, Cochrane and the WHO International Clinical Trials Registry platform. We included publications in any language. We also searched for grey literature published by the Emergency Nutrition Network (ENN), http://www.ennonline.net/.

Combinations of the following search terms were used (Figure 1; Annex 1):

"((Infant Nutrition Disorders) OR (wasting OR Wasting Syndrome[MESH]) OR (emaciation) OR (underweight) OR (malnutrition) OR (kwashiorkor) OR (marasmus) OR (marasmic kwashiorkor))"

AND

"((Hospitalization) OR (admission) OR (discharge) OR (treatment) OR (community health services))"

AND

"(All low and middle income, LMIC countries)" - please see appendix for full details.

limited to Humans, All Infant: birth-23 months.

After initial screening of titles, we reviewed the full text of potentially eligible studies and also checked reference lists for other potential papers.

3.2.2 Inclusion/exclusion criteria

We applied the following Population, Intervention, Comparator and Outcomes (PICO) framework:

- **P**opulation:
  severe malnutrition in infants aged <6m
- **I**ntervention:
  any treatment programme that includes supplemental feeding or similar dietary intervention
- **C**ontrol group:
  education/counselling/monitoring alone
- **O**utcomes:
  primary*:* mortality
  secondary*:* weight gain; nutritional recovery; reoccurrence of malnutrition.

Due to the paucity of literature, our inclusion criteria were wide and included observational as well as intervention studies, studies that include infants <6m and studies that report treatment outcomes (including mortality; nutritional recovery; weight gain; recurrence of malnutrition). We excluded studies not fulfilling inclusion criteria as well as case reports of individual patient outcomes and studies that did not specify which admission criteria were used for infants <6m.

4. Results

4.1 AGREE appraisal of national SAM guidelines – guideline summary

4.1.1 Origin and date

We identified guidelines from 36 countries, most of which (28/36, 78%) were from Africa (Table 1).

Table 1

Country guidelines included in the AGREE review

UN Region	Country	Language	Date of protocol
Eastern Africa (n=13)	Burundi	French	2010
	Djibouti	French	2009
	Ethiopia	English	2007
	Kenya	English	2008
	Madagascar	French	2009
	Malawi	English	2010
	Mozambique	Portuguese	2010
	Rwanda	English	2010
	Tanzania	English	2010
	Uganda	English	2010
	Zambia	English	2009
	Zanzibar	English	2010
	Zimbabwe	English	2008
Middle Africa (n=2)	Democratic Republic of the Congo	French	2008
	Central African Republic	French	Not stated
Southern Africa (n=1)	Botswana	English	2009
Western Africa (n=10)	Burkina Faso	French	Not stated
	Côte d'Ivoire	French	2010
	Ghana	English	2010
	Guinea	English	2008
	Mali	French	2008
	Mauritania	French	2009
	Niger	French	2009
	Senegal	French	2008
	Sierra Leone	English	2009
	Togo	French	2009
Northern Africa (n=2)	Sudan	English	2009
	South Sudan	English	2009
Asia (n=6)	Afghanistan	English	2008
	Bangladesh	English	2008
	India	English	2006
	Pakistan	English	2005
	Sri Lanka	English	2007
	Tajikistan	English	2009
Middle East (n=1)	Yemen	English	2008
The Americas (n=1)	Honduras	Spanish	2004

4.1.2 National Center for Health Statistics (NCHS) growth references or WHO-GS

To assess nutritional status, most of the 36 guidelines used World Health Organization Growth Standards (WHO-GS). Their use was more common in more recent guidelines:

- 20/36 (56%) were based on 2006 WHO-GS:
    - of those dated 2009 or later, 16/19 (84%) were based on WHO-GS;
- 13/36 (36%) were based on NCHS (used to refer to old growth references);
- in 2/36 (6%) it was not clear whether they were based on WHO standards or NCHS references.

Errors were noted in some of the guidelines:

- one guideline implied in the main text that it was based on WHO-GS and labelled the weight-for-height (W/H) look-up table in Annex 1 as such: but wrongly reproduces an NCHS table;
- one guideline stated that it used WHO-GS but referred to % of median rather than the z-score;
- one guideline referred to weight-for-length/height in the text but did not specify whether NCHS references or WHO standards should be used; in the annex, it included a WHZ (NCHS) table and, confusingly, a LAZ (WHO) table.

4.1.3 Case definition of SAM

There was uniform (36/36, 100%) agreement among guidelines that SAM, for the purpose of admission to treatment programmes, should be defined as low weight-for-length/height:

- <-3 z-scores – where WHO-GS used;
- <70% of median (or -3 z-scores) – where NCHS growth references used (in most cases, % of median is suggested as the preferred option).

Oedematous malnutrition was also recognized by all guidelines as defining SAM. All but two guidelines (both older and both from Asia) recognized mid-upper arm circumference (MUAC) as an independent criterion defining SAM for those aged >6months (or >65 cm in length). Again, errors were noted. Two guidelines based on WHO-GS suggested an associated MUAC of 110 mm rather than 115 mm. However, this would not affect infants <6m since no guideline currently recognizes MUAC as an indicator for this age group.

4.1.4 Recognition of infant <6m SAM

Of the 36 guidelines, 29 (81%) protocols had specific sections on SAM in infants <6m. A further two protocols recognized the problem but did not go into detail, implying the existence of other documents that covered the issue. Space devoted to infants <6m ranged from 2% to 19% (mean 8%) of total page count, excluding annexes (1–19%, mean 6% including annex pages).

4.1.5 Details of infant <6m treatment

To evaluate the appropriateness of admission/discharge criteria for infant <6m SAM, it is critical to first specify appropriateness *for what treatment*. Of the 29 guidelines that recognized infants <6m:

Inpatient vs outpatient care:

- 29/29 (100%) recommended inpatient care.

Details of treatment:

- 20/29 (69%) specified "improving or re-establishing exclusive breastfeeding" (or similar) as the core treatment objective; others did not specify an objective, but implied the same;
- 29/29 (100%) used supplementary suckling (SS) as the core treatment methodology;[1]
- 23/29 (79%) divided infants into two distinct groups:
    - those with a possibility to breastfeed;
    - those with no possibility of breastfeeding (e.g. orphans with no mother);
- 5/29 (17%) did not directly address infants with no possibility of breastfeeding;
- 1/29 (3%) did not seem to recognize that there may be infants who had no possibility of breastfeeding (this protocol talked about re-lactation of other female carers such as an aunt).

[1] This is a treatment whereby the infant continues to breastfeed, but receives "top-up" milk via a tube held alongside the nipple. The rationale is to supplement intake while simultaneously stimulating an increase in breast milk production. As breast milk production increases, the supplement is gradually withdrawn until breast milk alone is providing for sufficient growth.

4.1.6 Infant <6m admission criteria

Anthropometric admission criteria

All protocols that noted infant <6m SAM defined it as using the same W/H anthropometric criteria as for older children i.e. WHZ <-3 (WHO or NCHS) or WHM <70% (NCHS).

MUAC was not recommended for infants <6m in any of the guidelines.

Clinical admission criteria

Clinical admission criteria were noted in all the protocols focusing on infants <6m. Either implicitly or, in most cases explicitly, these were independent of W/H, so would lead to admission even if the W/H were within normal range. Though phrased slightly differently in different protocols, these can be summarized as:

- infant too weak or feeble to suckle effectively (independent of W/H);
- infant not gaining (or losing) weight at home;
- mother has insufficient breast milk.

Despite this emphasis on effective breastfeeding, only two protocols had guidance on how to assess breastfeeding. Only one cited a formal breastfeeding assessment tool but did not specify a threshold score for admission.

Three guidelines also cited "visible wasting" as an independent admission criterion.

4.1.7 Other groups treated with the infant <6m protocol

As well as infants <6m, other infants were noted as eligible for treatment using infant <6m guidelines (rather than guidelines for older children). No guidelines specified a minimum age (i.e. whether also applicable to neonates, as well as older infants <6m) but other admission criteria were:

- infants weighing <4 kg (n=6, 21% of infant <6m protocols)
- infants weighing <3.5 kg (n=2, 6% of infant <6m protocols)
- infants weighing <3 kg (n=17, 59% of infant <6m protocols)

4.1.8 Discharge criteria for infants <6m

There were two sets of discharge criteria:

For infants <6m with the possibility of being breastfed

All but one protocol focused on effective breastfeeding, judged by weight gain, as indicating that an infant was ready for discharge home. Details of how this was expressed varied according to whether or not a time period was specified:

- 17/29 (58%) once gaining weight on breastfeeding alone (no SS):
    - minimum 20 g/day was specified in one protocol;
    - minimum length of stay in programme of not less than 21 days was specified in one protocol;
- 1/29 (3%) once gaining weight on breastfeeding alone (no SS) for three days;
- 10/29 (34%) once gaining weight on breastfeeding alone (no SS) for five days:
    - minimum 20 g/day was specified by one protocol.

In all these cases, discharge was independent of actual weight-for-length (W/L). Only one (old 2004 protocol) specified that the infant should be >80% W/L (NCHS).

For infants <6m with no possibility of being breastfed

There was greater variation in how this was expressed. In general, the discharge criterion mirrored that for older children and focused on achieving a weight-for-height/length target:

- 2/29 (7%) 20% weight gain (from admission weight);
    - 1/29 (3%) or >-1 weight-for-length z-scores (WLZ);
- 1/29 (3%) 15–20% weight gain;
- 6/29 (21%) 15% weight gain;
- 3/29 (10%) >-1 WLZ;
- 3/29 (10%) >-2 WLZ;
- 4/29 (14%) W/L >85% median;
- 1/29 (3%) W/L >80–85% median;
- 2/29 (7%) W/L >80% median;
- 7/29 (24%) not specified or other.

4.2 AGREE appraisal of national SAM guidelines – guideline quality

The 29 guidelines that included infants <6m were rated according to the AGREE framework.

4.2.1 Scope and purpose (AGREE Domain 1)

This comprised three different items:

- overall objectives specifically described;
- clinical questions clearly described;
- patient group clearly described.

These items were all clearly covered. For all three items:

- Mean AGREE score = 4.00:
  - AGREE score 4/4 n=29 guidelines, 100%

4.2.2 Stakeholder involvement (AGREE Domain 2)

Guideline development group included individuals from all the relevant professional groups

- Mean AGREE score = 3.03:
  - AGREE score 4/4 n=12 guidelines, 41%
  - AGREE score 3/4 n=6 guidelines, 21%
  - AGREE score 2/4 n=11 guidelines, 38%
  - AGREE score 1/4 n=0

In most cases, the guideline development group was clearly described and represented a broad range of professional groups. These ranged from ministries of health, to United Nations (UN) organizations – WHO, the United Nations Children's Fund (UNICEF) – to international nongovernmental organizations (NGOs) to local NGOs and local health-care professionals. Some guidelines neglected to identify which organizations were represented by named individuals or by only having minimal details of the development group.

Patients views and preferences should be sought

- Mean AGREE score = 1.00:
  - AGREE score 4/4 n=0
  - AGREE score 3/4 n=0
  - AGREE score 2/4 n=0
  - AGREE score 1/4 n=29 guidelines, 100%

None of the guidelines indicated having solicited and obtained patient input.

Target users clearly defined

- Mean AGREE score = 3.31:
  - AGREE score 4/4 n=9 guidelines, 31%
  - AGREE score 3/4 n=20 guidelines, 69%
  - AGREE score 2/4 n=0
  - AGREE score 1/4 n=0

One third of guidelines clearly stated who their target audience was. The others implicitly targeted health-care professionals and managers dealing with SAM.

Guideline piloted among end users

- Mean AGREE score = 3.03:
  - AGREE score 4/4 n=1 guideline, 3%
  - AGREE score 3/4 n=28 guidelines, 97%
  - AGREE score 2/4 n=0
  - AGREE score 1/4 n=0

Only one guideline noted local piloting. This does not, however, mean that the guidelines were untested. All had many similarities and were based on a "evolutionary common ancestor", a generic SAM guideline that has been extensively used in many settings over many years.

4.2.3 Rigour of development (AGREE Domain 3)

Systematic methods should be used for search of evidence

Criteria for selecting the evidence should be clearly described

Methods for formulating the recommendations should be clearly described

For all these items:

- Mean AGREE score = 1.00:
  - AGREE score 1/4 n=29 guidelines, 100%

Nowhere was the process of guideline development and evidence selection described in any detail. To put this observation in context, it should be noted, however, that all the guidelines described were meant for front-line field use. Arguably, the process of development would not have been appropriate content for the audience.

Health benefits, side effects and risks considered

- Mean AGREE score = 3.00:
  - AGREE score 3/4 n=29 guidelines, 100%;

Though all guidelines highlighted the benefits of treatment, all had limited mention of side-effects and risks.

There should be explicit links between recommendations and supporting evidence

- Mean AGREE score = 1.21:
  - AGREE score 4/4 n=0
  - AGREE score 3/4 n=3 guidelines, 10%
  - AGREE score 2/4 n=0
  - AGREE score 1/4 n=26 guidelines, 90%

Three guidelines stood out for at least proving extensive references as footnotes of each section.

Guidelines should be externally reviewed by experts prior to publication

- Mean AGREE score = 2.83:
  - AGREE score 4/4 n=6 guidelines, 21%
  - AGREE score 3/4 n=12 guidelines, 41%
  - AGREE score 2/4 n=11 guidelines, 38%
  - AGREE score 1/4 n=0

This was variably done. Only a minority of guidelines was clear about which of the listed individuals were authors and which were reviewers of the guidelines. It was often not possible to tell who had taken which role in the development process. In 11 cases, the development team was not detailed at all.

A procedure for updating the guidelines should be provided

- Mean AGREE score = 1.14:
  - AGREE score 4/4 n=0
  - AGREE score 3/4 n=2 guidelines, 7%
  - AGREE score 2/4 n=0
  - AGREE score 1/4 n=27 guidelines, 0%

All but two guidelines had no explicit process for update. Even where it was noted, the specifics were vague.

4.2.4 Clarity and presentation (AGREE Domain 4)

Recommendations should be specific and unambiguous

- Mean AGREE score = 3.66:
  - AGREE score 4/4 n=20 guidelines, 69%
  - AGREE score 3/4 n=8 guidelines, 28%
  - AGREE score 2/4 n=1 guideline, 3%
  - AGREE score 1/4 n=0

Most guidelines were either clear or very clear in their recommendations. Only one was scored below 3 – this was a draft guideline with a very long text that made it very difficult to pick out key recommendations.

Different options for diagnosis and treatment of the condition should be presented

- Mean AGREE score = 3.00:
  - AGREE score 3/4 n=29 guidelines, 100%

All guidelines offered a limited range of treatment options.

Key recommendations should be easily identifiable

- Mean AGREE score = 3.48:
  - AGREE score 4/4 n=14 guidelines, 48%
  - AGREE score 3/4 n=14 guidelines, 48%
  - AGREE score 2/4 n=1 guideline, 4%
  - AGREE score 1/4 n=0

Only one guideline scored below 3. Almost half the guidelines scored 4/4, with clear tables and flow charts helping users identify key recommendations.

Guidelines should be supported with tools for application

- Mean AGREE score = 3.89:
  - AGREE score 4/4 n=27 guidelines, 92%
  - AGREE score 3/4 n=1 guideline, 4%
  - AGREE score 2/4 n=1 guideline, 4%
  - AGREE score 1/4 n=0

Almost all guidelines contained an extensive array of tools for application. These varied between different guidelines but included patient education materials, clinical care charts and programme monitoring charts.

4.2.5 Applicability (AGREE Domain 5)

Potential organizational barriers in applying recommendations should be considered

- Mean AGREE score = 3.48:
  - AGREE score 4/4 n=15 guidelines, 52%
  - AGREE score 3/4 n=13 guidelines, 45%
  - AGREE score 2/4 n=1 guideline, 3%
  - AGREE score 1/4 n=0

The best guidelines contained annex contents that would help overcome organizational barriers to guideline application, e.g. details job descriptions for key staff.

Potential cost implications of applying the recommendations should be considered

- Mean AGREE score = 1.00:
  - AGREE score 1/4 n=29 guidelines, 100%

None of the guidelines explicitly considered cost of implementation. This is arguably unnecessary for guidelines aimed at front-line field workers. Even if considered, any costing information would risk going out of date very quickly with often volatile economies and exchange rates.

Guidelines should present key review criteria for monitoring and audit purposes

- Mean AGREE score = 3.69:
  - AGREE score 4/4 n=21 guidelines, 72%
  - AGREE score 3/4 n=7 guidelines, 24%
  - AGREE score 2/4 n=1 guideline, 4%
  - AGREE score 1/4 n=0

Most guidelines described clear monitoring and evaluation methods and criteria. Relevant to infants <6m, a number of programme reporting sheets did not allow for this group to be separately identified and their outcomes monitored because they were grouped with others such as children aged >60 months with medical complications.

4.2.6 Editorial independence (AGREE Domain 6)

Guidelines should be editorially independent from the funding body

- Mean AGREE score = 1.00:
  - AGREE score 1/4 n=29 guidelines, 100%

None of the guidelines described this issue. While in the context of SAM it is unlikely that any issues would arise, it is important to note that organizations funding the process of guideline development often have a dual role in that they also employ technical experts and facilitate technical inputs.

Conflicts of interest of guideline development members should be recorded

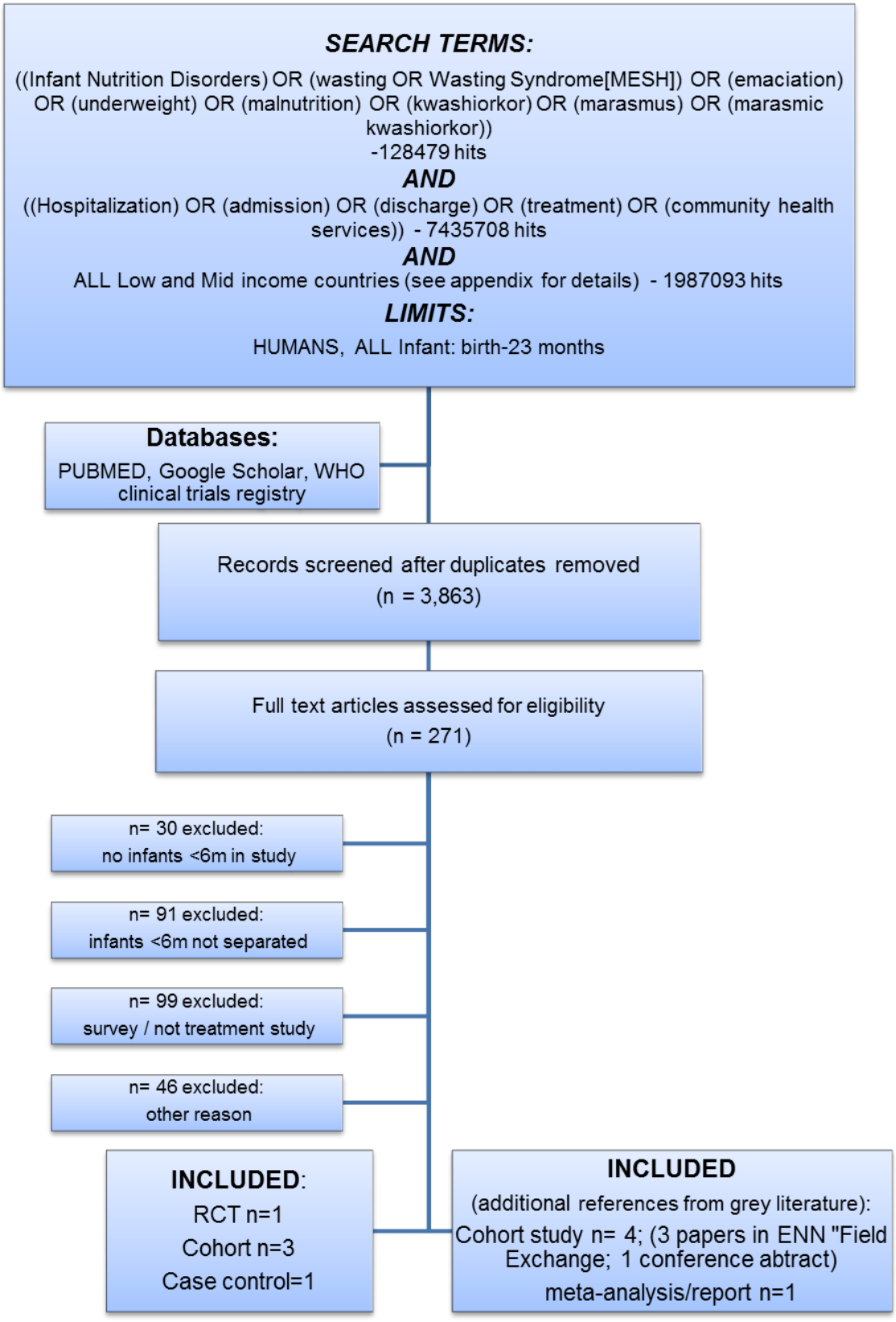
- Mean AGREE score = 1.00:
  - AGREE score 1/4 n=29 guidelines, 100%

None of the guidelines included a statement of conflict of interest.

4.3 Review of published literature

Figure 1

Flow chart for study selection



4.3.1 Question 1: Is outpatient-based care possible for infant <6m SAM?

A 1994 randomized controlled trial (RCT) from Niger compared ambulatory care to hospital care for 100 malnourished children with 6% "5 or 6 months of age" (*7*). While overall results found no significant differences in mortality or weight gain, a more cost-effective ambulatory programme, no infant <6m subanalysis was presented (i.e. overall outcomes were reported, but infant <6m specific outcomes were not). Even if infant outcomes had been noted, numbers would have been too small to make any reliable inferences.

No other directly relevant studies were found on this question.

4.3.2 Question 2: For malnourished infants <6m, what is the value of treatment at a variety of admission criteria?

A 2008 cohort study of SS in Afghanistan examined outcomes on 94 children admitted with a variety of different admission criteria (*8*):

- infant <6m SAM (oedema, n=8; W/H <70% [NCHS], n=21);
- age <6 months and weight <4 kg, n=6;
- length <49 cm and age <6 months, n=27 –(note that NCHS growth references only went down to length 49 cm, hence this groups' W/L median could not be assessed);
- moderate malnutrition (70–80% median W/L) *and* maternal milk insufficiency (MMI), n=26;
- no malnutrition but MMI, n=3;
- MMI but anthropometric status unknown, n=3.

For each of the above groups, cure and death were the main outcomes determined. Overall cure was 61/94 (64.9%) and deaths were 7/94 (7.4%). As well as having small numbers in each group – with high consequent risk of both bias and confounding – an additional problem in this study was heterogeneity in the definition of cure. Whereas centre protocols define cure as "discharge on breastfeeding alone", it emerged that only 16/55 (29%) of "cures" fully met this criterion. Some of the centres in the study were (wrongly) discharging children with continued milk supplements given to take home.

A 2009 RCT from the Democratic Republic of Congo and Niger (*9*) used standard admission and discharge criteria as already identified by the AGREE section of this review:

- admission: <70% W/L (NCHS) *or* infant too weak or feeble to suckle effectively *or* mother reports breastfeeding *or* mother reports that infant is not gaining weight at home;
- discharge: gaining weight (10 g/day for three to five consecutive days on breastfeeding).

Since only one set of admission/discharge criteria was used, (the RCT comparator being type of milk once admitted to the programme) for the purposes of this review this RCT counts as a cohort study. Overall cure rate in this study was 98/146 (67%) and overall mortality rate 23/146 (16%).

A 2000 study of SS recruited 25 infants using the following criteria (*10*):

- admission: - <70% W/L (NCHS);
- discharge: once >85% W/L and four days on EBF.

Following these criteria and with SS as the main treatment, 16 (64%) infants were successfully discharged and 5 had to be referred to the local hospital.

A 2011 study in South Africa examined outcomes in a population where HIV was common underlying SAM (*11*). SAM was defined as:

- oedema and/or WHZ <-3 (WHO);
  or
- oedema and/or weight-for-age (W/A) <60% (Wellcome Classification, which looks at % of expected W/A as the criterion for defining malnutrition).

Infant-specific outcomes were not presented. While univariable analysis suggested that younger age was a risk factor for death, this was not confirmed in a multivariable model.

A 2009 study from Bangladesh enrolled 60 malnourished children aged 2–59 months using admission criteria of <70% weight-for-length/height (NCHS references) ± oedema (*12*). It allocated them to two different feeding groups and while it did report discharge/mortality outcomes for the two feeding groups, it did not report age-specific mortality. It did, however, find that growth rate depended on age and that this in turn differed according to the feeding group, though non-significantly so.

A 2002 study of hospital inpatients in Burkina Faso (*13*) included 272 infants <6m of a total of 1573 children aged <5 years. Of these, 6.7% had a weight-for-age <-3 z-score (WAZ). Compared to the reference age group 36–59 month olds, adjusted odds ratio for death was 4.2 (95% CI 2.4 to 7.3).

A 2008 study from Colombia described in detail the nutritional profile of infants <6m who were admitted: 7/56 (12.5%) with marasmus and 49/56 (87.5%) with kwashiorkor (*14*). Yet again, however, infant-specific outcomes were not reported.

The only study identified that looked at alternative admission criteria was presented as an abstract at a 2009 meeting (*15*). It is one of the most important pieces of evidence towards this review and is worth quoting in detail. It looked at 3432 Kenyan infants aged 2–6 months and found that MUAC at admission "performed at least as well in predicting inpatient death (ROC area under the curve 0.76 to 0.82, depending on age) as among children aged 6–60 months and at least as well as WLZ. MUAC <11 cm occurred in 19% of infants aged 2–6 months and was associated with case fatality of 22 to 23% (depending on age) compared to case fatality of 3–5% for MUAC ≥11 cm ($p<0.001$, relative risk 6.64 [95% CI 4.08 to 10.8]); 10–17% of those with MUAC <11 cm were bacteraemic compared to <5% of those with MUAC >11 cm bacteraemic ($p<0.001$). Relative risks were not diminished by adjustment for HIV antibody status or history of prematurity. Among infants discharged alive, one-year survival was strongly associated with admission MUAC".

Finally, there are two important meta-analyses on this issue, both presented in the MAMI project (*4*). As with all the studies noted above, none directly compares outcomes in the same programme using different admission criteria. Rather, they compare:

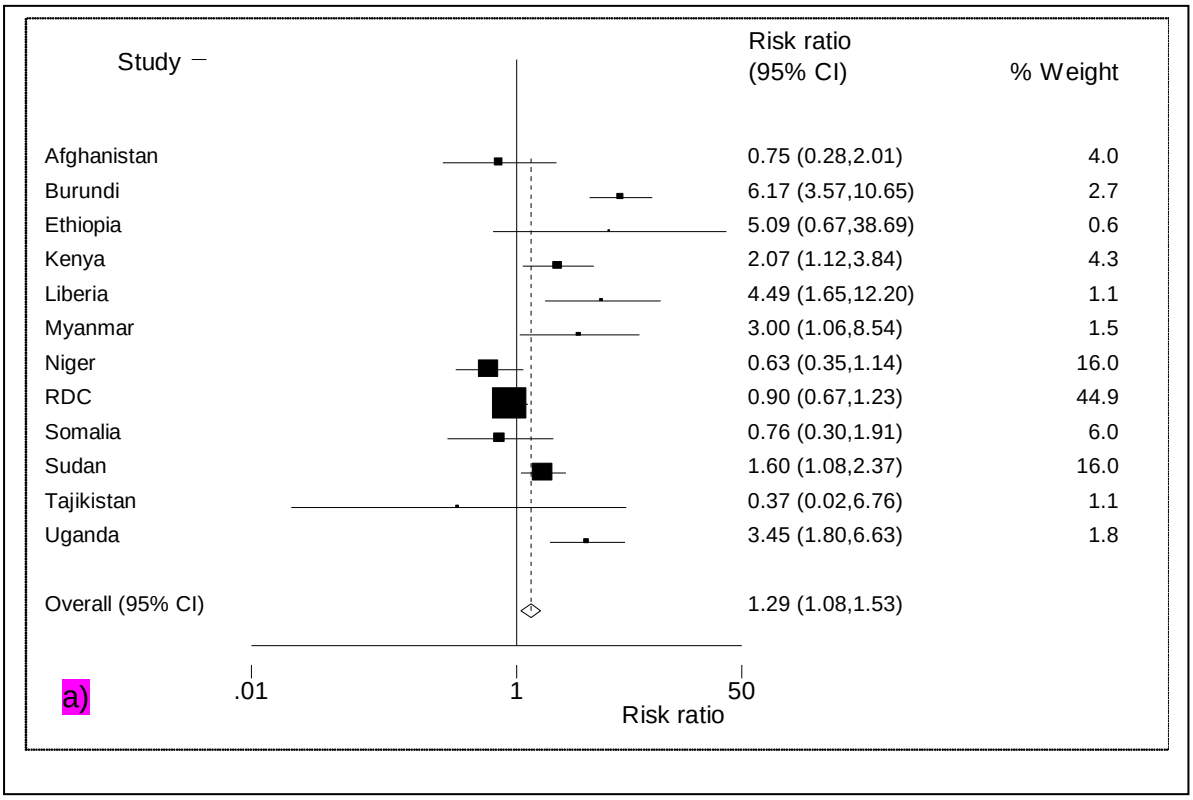
- programmes run by the same NGO, Action Against Hunger, in 12 different countries, thereby controlling for protocols/treatment albeit imperfectly;
- programmes run in the same country, Burundi, by a number of different organizations, thereby controlling for country albeit imperfectly.

Forest plots from these two analyses are shown below (Figures 2 and 3). For both, pooled mortality among infants <6m was significantly higher than among 6 to <60m olds. It is important to note,

however, that there is important heterogeneity between individual sites. While a similar protocol and admission/discharge criteria were used for all, how they were implemented on the ground varied. Qualitative work in another chapter of MAMI found, for example, that in some settings, infants would be brought in very late, whereas in other settings, they would present much earlier, when clinically less sick and vulnerable.

Figure 2

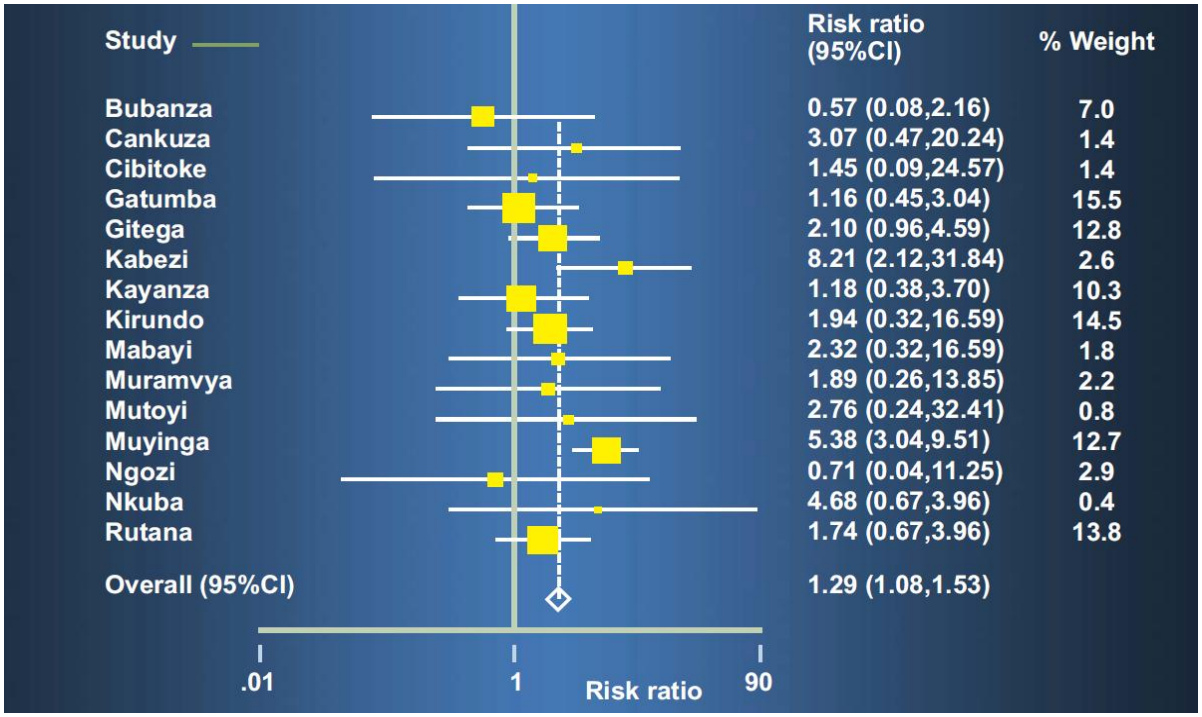
Risk of death of infants <6m compared to children 6–59 months in 12 countries



RDC = DRC (Democratic Republic of the Congo)
Source: MAMI project (http://www.ennonline.net/pool/files/ife/mami-report-chapter-5-review-of-field-treatment.pdf, accessed 18 October 2011).

Figure 3

Risk of death of infants <6m compared to children 6–59 months in different programmes in Burundi



Source: MAMI project (http://www.ennonline.net/pool/files/ife/mami-report-chapter-5-review-of-field-treatment.pdf, accessed 18 October 2011).

4.3.3 Question 3: For malnourished infants <6m, what discharge criteria have been used to determine the optimal time to conclude feeding/dietary interventions?

No studies were identified comparing treatment programme outcomes using different discharge criteria. Several cohort studies, noted in the section above, also described discharge as well as admission criteria.

4.3.4 Other relevant papers

During the course of this review, three other key pieces of evidence were identified:

- **Interpretation of new WHO growth charts and growth trend among infants <6m**

  WHO-GS are currently being rolled out internationally and are technically superior. They do, however, have important differences from NCHS references (*14,15*). One is that more infants <6m fall below standard anthropometric thresholds for undernutrition. It has been suggested that because of this, using WHO standards to assess infants <6m risks "doing more harm than good" (*16*): health-care workers or carers might inappropriately interrupt EBF over concerns that a small but clinically well infant is getting "insufficient milk" (*16*). While controversial, this potential risk does appear to be supported by available evidence: in a randomized

crossover trial involving 79 health-care workers from 6 randomly sampled centres in southern Malawi, participants showed increased concern (McNemar's Test, $p<0.01$) when growth was plotted on the WHO charts rather than on NCHS charts. They were also 2.4 times more likely to refer or admit ($p<0.05$) and 1.5 times more likely to counsel practices that interrupt EBF ($p<0.05$). Even when a favourable growth trend line was shown, this made no difference to level of concern, referral or feeding advice (*17*).

- **Identification of breastfeeding problems in infants <6m**

A chapter of the MAMI report was devoted to assessing breastfeeding so that the root cause of any problems might be properly identified and addressed. Many tools were found but the report concluded that:

> "No one tool was identified as sufficiently sensitive for community use and specific for use in inpatient settings. Quality research studies to test the validity of existing breastfeeding assessment tools in different settings are needed. In the interim, UNICEF b-r-e-a-s-t, the UNICEF 2006 breastfeeding observation aid and the aids described in IFE Module 2 can be used to assess breastfeeding in programmes managing infants <6m. Severe maternal wasting and maternal and infant HIV status are just two of the important wider considerations when assessing breastfeeding effectiveness" (*4*).

- **Identification of clinical problems in infants <6m**

Distinguishing an infant who is at immediate risk of mortality from one who is more stable is critical to effective referral and appropriate treatment. A recent paper has highlighted which clinical signs best identify severe illness in infants aged 0–59 days (*18*). This offers an important template (albeit one that needs extension to 2–6 month olds).

5. Discussion and conclusions

5.1 Summary of main findings and issues arising

The main finding of this review is that evidence – of any quality – on infant <6m SAM is limited. Existing country guidelines on the management of infant <6m SAM have many strengths in terms of key AGREE domains (clarity of scope and purpose; engagement with professional stakeholders; clarity of presentation; provision of support materials). Their major weakness, however, is that they are not based on high-quality evidence.

Paucity of evidence to make *strong* recommendations does not mean that *no* recommendations can be made. It is important to note that:

- current guidelines cannot be viewed as a "Gold Standard" since they are not based on gold standard evidence; there is more than one way to develop a diagnostic criteria:
    - a normative approach, based on statistical deviation from a range – which is what currently takes place;
    - a risk approach – which sets criteria according to observed risk;
    - a risk–benefit approach – which takes into account the relative risks as well as benefits of a specific treatment associated with the diagnostic criterion.
- the care of children aged 6–59 months underwent a radical shift from a highly medicalized inpatient-only model of care to a public health, community-based system without high-quality RCT evidence supporting the move; with this in mind, this review concludes with four risk–benefit recommendation tables that synthesize evidence on (Tables 2–5):
    - Where we are now:

      – in terms of what current national guidelines are recommending.
    - What the key issues are:

      – in light of evidence referenced in this report and other associated literature.
    - Where do we want to be in future:

      – highlighting key areas for future research and policy change.

5.2 Risk–benefit summary tables

5.2.1 Outpatient treatment of infant <6m SAM

This is consistent with the suggestion from the AGREE guideline review that inpatient treatment is the current standard of care. However, the absence of evidence on this question also affects the applicability of the predefined PICO framework to tackle the other review questions – these require that an intervention group of infants <6m with SAM be compared against a control group receiving only education/counselling/monitoring.

Table 2

Risk–benefit summary table for outpatient treatment of uncomplicated infant <6m SAM

Existing recommendation/practice All infants <6m with SAM are treated as inpatients.	
Proposed recommendation/practice Treatment sites with the capacity for closely monitored research/operational research should consider harmonizing infant <6m SAM treatment with that of older children; namely, infant <6m SAM should be divided into: • complicated SAM - which would continue to be treated in inpatient settings using current protocols; • uncomplicated SAM - which could be treated in the community through provision of community-based interventions such as breastfeeding support groups/empirical antibiotics.	
Quality of evidence (for outcomes deemed critical)	Low There is currently an absence of evidence showing that outpatient-based treatment is effective and safe. Balancing this, there is also no evidence that inpatient care is necessary for all infant <6m SAM.
Benefits/desired effects	Increased programme capacity to treat infants <6m. If programme capacity is increased, there is more scope for active case finding of infants <6m, for greater coverage of this age group and for greater public health impact of treatment programmes. Lower cost per patient (assuming that outpatient costs are lower than inpatient costs).
Risks/undesired effects	The safety of outpatient treatment for infant <6m SAM is not yet established – hence, the need to closely formally evaluate/closely monitor any such project.
Values/acceptability	Many professionals/professional groups currently would be reluctant to accept outpatient treatment of infant <6m SAM (as was the case when CMAM for 6–59 month olds was first proposed). Carers value outpatient-based treatments and may be likely to present *more* readily for care at an earlier stage of illness – due to lower opportunity costs of programme attendance.
Costs	If programme coverage increases, total programme cost may increase even if cost per patient (cost-effectiveness) improves.
Feasibility	Outpatient care for infants <6m is feasible but when first piloted will require high-quality technical/logistical inputs to demonstrate safety.
Final recommendation	Research/operational research programmes should consider trialling outpatient-based care of infant <6m SAM.
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Conditional (needs to be the right setting)
Quality of evidence that	*High/Moderate/Low/Very Low*

informs recommendation	Low
Comments justifying recommendation	Using a case definition of WHZ <-3 (WHO growth references), 3.8 million infants <6m worldwide have SAM (of a total 20 million 0 to <60 month olds with SAM globally). This represents a large increase over numbers defined by old NCHS growth standards (0.8 million SAM infants, out of a total 9.3 million 0 to <60 month olds with SAM) (*6*). The MAMI project clearly highlighted that many programmes struggled to deal with relatively small numbers of infant <6m SAM. To cope with the increased numbers defined using WHO-GS, a radical shift in approach is necessary. It is also necessary because inpatient-only treatment is an increasing anomaly in a world that recognizes the difference between complicated and uncomplicated SAM. It is important to recognize that inpatient-based care is itself associated with risk (e.g. nosocomial infection; interruption of EBF; financial and social burden on family) so the current model of care should not be assumed to be automatically more or less safe than the proposed complicated/uncomplicated model of care.
Gaps, research needs, comments	Safety, effectiveness and cost-effectiveness of this approach needs to be tested in a variety of different contexts.

5.2.2 Anthropometric admission criteria for infant <6m SAM

Table 3

Risk–benefit summary table for anthropometric admission criteria for infant <6m SAM

Existing recommendation/practice All guidelines recognize the same weight-for-length (W/L) anthropometric criteria for infant <6m SAM as for children 6 to <60m SAM (but use a wide range of possible options, ranging from WLZ NCHS to WLM NCHS to WLM WHO).	
Proposed recommendation/practice • Research is needed to optimize admission criteria and to link them more clearly to risk–benefit profiles of different treatments (e.g. sensitive criteria are suitable for admission to low-risk outpatient-based breastfeeding support whereas more specific indicators are needed for admission to treatments such as SS that have greater inherent risks). • For the short to medium terms, WLZ <-3 (WHO standards) is suitable for infants and should be continued (noting however risks of inappropriate interruption of EBF in clinically well infants <6m who are breastfeeding well). • MUAC-based criteria (e.g. using <11 cm to define SAM) should be considered urgently for infants aged 2–6 months.	
Quality of evidence (for outcomes deemed critical)	Very Low There is no evidence that the case definition of SAM based on WHO standards is superior to other case definitions. Evidence on MUAC is available but needs to be repeated in other settings and explored in parallel with research on treatment.
Benefits/desired effects	Harmonize and standardize admission criteria between programmes so that lessons can be learnt though a more valid inter-programme comparison of consequent outcomes. WHO standards go down to a length of 45 cm (whereas NCHS only went to 49 cm) – it will be possible to calculate a valid W/L for more infants than before. More infants eligible for and enrolled in treatment programmes (note that this is only a benefit if they have a need for/will benefit from treatment – this needs to be better demonstrated – the flip side of this is overdiagnosis which is a risk rather than a benefit).
Risks/undesired effects	A greater number of infants overwhelms already limited treatment programme capacity. Using WHO-GS, specificity risks being compromised - carers of clinically well, normally breastfed children may become more anxious about growth and may wrongly interrupt EBF (*16,17*).
Values/acceptability	There is widespread international agreement and "buy-in" to adopt the new WHO-GS. Some carers may value the lower threshold to treatment for infants <6m. Some carers may not value the lower treatment thresholds (especially if treatment involves prolonged inpatient admission with all the associated costs).
Costs	As more infants <6m become eligible for treatment, total programme costs will increase.
Feasibility	Programme capacity to care for the larger number and proportion of infants <6m must be supported through greater resource inputs.
Final recommendation	Programmes adopt case definitions of infant <6m SAM based on

	WHO-GS.
Strength of recommendation	*Strong **OR** Conditional **OR** Qualified **OR** Weak* Conditional (since it remains to be proven what the mortality risks associated with current cut-offs is)
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Comments justifying recommendation	Global rollout of WHO standards is proceeding fast and should be supported.
Gaps, research needs, comments	MUAC-based and other screening criteria for infant <6m SAM should be explored to enable active community case finding (W/L measurement is not practical in routine field settings or where rapid population/individual assessment is needed).

5.2.3 Clinical admission criteria for infant <6m SAM

Table 4

Risk–benefit summary table for clinical admission criteria for infant <6m SAM

Existing recommendation/practice All guidelines recommend clinical features such as "too weak or feeble to suckle effectively" as independent admission criteria to infant <6m SAM treatment programmes.	
Proposed recommendation/practice • The importance of independent clinical admission criteria to treatment programmes that seek to improve or re-establish EBF should be reaffirmed and further emphasized. • Most settings should continue using current guidelines since most already recognize plausible clinical criteria. • Settings with the capacity for research/operational research should set up studies and audit to more formally test and evaluate different clinical criteria, e.g. underlying disease in the infant *and* mother (e.g. tuberculosis, HIV); underlying disability in the infant *and* mother (e.g. maternal depression/mental health problems).	
Quality of evidence (for outcomes deemed critical)	Very Low There is no hard evidence to support any one set of clinical criteria cited in current SAM guidelines.
Benefits/desired effects	In the long term, the quality of clinical criteria should be enhanced so as to optimize: • sensitivity (admission for those who will benefit from treatment); • specificity (avoiding unnecessary admissions).
Risks/undesired effects	Suboptimal clinical criteria may either: • miss infants who would benefit from treatment (low sensitivity); • needlessly treat those who do not stand to benefit (low specificity).
Values/acceptability	Optimizing the specificity and sensitivity of programme admission criteria would benefit patients, families, programme staff and programme funders.
Costs	Better-performing admission criteria should lead to better programme cost-effectiveness.
Feasibility	Research/audit inputs are needed to refine current clinical admission criteria.
Final recommendation	Carry on with current clinical criteria as cited in existing guidelines Lobby hard for new research in this area.
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Strong
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Comments justifying recommendation	
Gaps, research needs, comments	See above; safety, efficacy and cost-effectiveness of any new assessment tool needs to be thoroughly tested.

5.2.4 Discharge criteria for infant <6m SAM

Table 5

Risk–benefit summary table for discharge criteria for infant <6m SAM

Existing recommendation/practice Current guidelines recommend a large range of discharge criteria ranging from unspecified "weight gain" to reaching a z-score target weight; to increasing weight by 15–20% on admission weight.	
Proposed recommendation/practice • Programmes should continue with whatever is currently recommended by national guidelines; there is great equipoise and no good reason to favour one criterion over another. • Programmes with research/operational research capacity should trial different criteria used in the same programme.	
Quality of evidence (for outcomes deemed critical)	Very Low
Benefits/desired effects	In the long term, the quality of discharge criteria should be enhanced so as to optimize: • sensitivity (keeping vulnerable infants in the programme for long enough to benefit from treatment); • specificity (avoiding unnecessarily long stays in the programme).
Risks/undesired effects	Suboptimal discharge criteria may either: • prematurely discharge infants who would benefit from continued treatment (low sensitivity); • needlessly continue to treat those who have no further need of treatment (low specificity).
Values/acceptability	Optimizing the specificity and sensitivity of programme discharge criteria would benefit patients, families, programme staff and programme funders.
Costs	Better performing discharge criteria should lead to better programme cost-effectiveness.
Feasibility	Research/audit inputs are needed to refine current clinical admission criteria.
Final recommendation	Carry on with current criteria as cited in existing guidelines Lobby hard for new research in this area
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Strong
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Comments justifying recommendation	–
Gaps, research needs, comments	See above; safety, efficacy and cost-effectiveness of any new discharge protocol needs to be thoroughly tested.

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Annex 1 Low- and middle-income country (LMIC) search terms

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