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Home-based management of severely acute malnutrition: feasibility of ethically designed, community-based randomised clinical trials

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Abstract

The Indian Council of Medical Research had, on May 31, 2011, called for research proposals on severely acute malnourished (SAM) children to generate evidence for the development of practical and scalable regimens to medically rehabilitate children suffering from SAM, without serious complications, at the home/community level and/or peripheral inpatient facilities. The primary outcomes of the proposed research study are recovery from SAM in the short term, as well as sustenance of recovery (for at least six months after the initiation of treatment). The secondary outcomes are the acceptability, feasibility and safety of the regimes being tested. It was suggested that the studies be designed as individual or cluster randomised or quasi randomised controlled trials (RCTs). This paper analyses the methodological, operational, and most importantly, ethical challenges and implications of conducting community-based RCTs involving SAM children. The paper dwells in detail on why and how the RCT design is inappropriate and unsuitable for studying the effectiveness of home-based management of SAM children in the community.

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Introduction

Throughout the developing world, malnutrition is a major public health problem, accounting for nearly 50% of the deaths of the 10–11 million children under 5 years of age (1). In India, about 6.4% of children below the age of 60 months are suffering from severe acute malnutrition (SAM) (weight-for-height less than –3SD), according to the National Family Health Survey-III conducted in 2005–2006 (2). In the developing world, the risk of mortality among SAM children is directly proportional to the severity of the condition (3, 4). Over the years, the case fatality rate for malnutrition in health facilities has been 20–30% in the case of marasmus and up to 50–60% in that of kwashiorkor (5,6).

The Indian Council of Medical Research (ICMR) had called for research proposals on SAM children to generate evidence for the development of practical and scalable regimens to medically rehabilitate children suffering from SAM, without serious complications, at the home/community level and/or peripheral inpatient facilities. The primary outcomes of the proposed research study were to include recovery from SAM in the short term, as well as sustenance of recovery (for at least six months after the initiation of treatment). The secondary outcomes were to include the acceptability, feasibility and safety of the regimes being tested. The studies could be designed as individual or cluster randomised or quasi randomised controlled trials (RCTs). Letters of intent were solicited by the ICMR in the following areas.

1. An operationally feasible approach to identify children in

the community who have SAM, without complications, using the community workers and resources currently available

2. A comparison of the different therapeutic regimes (including the components of dietary, nutritional and supportive care) being used in the community and peripheral health facilities for the management of SAM without complications.
3. Indigenous development of product(s) suitable for the rehabilitation of SAM children.
4. The development of a stable and acceptable mixture of multi-micronutrients and minerals for use as a part of regimes for the management of SAM (7).

Discussion

Home-based management of SAM children is fast gaining importance in India and other developing countries as it has inherent advantages that can be exploited by community-based programmes. There is some evidence to show that home-based management is acceptable and cost-effective, and does help to reduce morbidity and mortality (8–13). In recent times, there have been two consensus statements emphasising the need to treat SAM children without complications at home (14,15). According to the current recommendations of the World Health Organisation (WHO), patients with SAM should first be managed at a referral centre for initial stabilisation, and this should be followed by home therapy (1). However, on the basis of evidence gathered from across the world, WHO has suggested that uncomplicated forms of SAM be treated in the community (16). One of the methods that have been suggested is the use of "therapeutic nutrition products", to be administered to children at home (17).

Public health justification for home-based management of SAM

The majority of national and international reviews have strongly advocated home-based management of SAM children as it essentially emphasises the promotion of preventive and promotive health. It also indirectly helps to prevent the commercialisation of malnutrition through nutrition therapy based on the products of multinational companies. Most importantly, it addresses the underlying social determinants of health, ie poverty, social exclusion, poor public health and loss of entitlement (18). There are several factors that favour experimentation with home-based management of SAM. First, more than 85% of all SAM cases do not have medical complications. Second, SAM children can be easily identified through active case-finding in the community. Global evidence also suggests that with community-based management, the case fatality rates among SAM children could be reduced to less than 5% (2).

The need for RCTs

Conceptually, home-based management is logically appealing and relevant to India. However, keeping in mind the tenets of evidence-based practice of public health, it is vital to critically evaluate the evidence available on home-based management of SAM. It is to be noted that most of the evidence on the effectiveness of home-based management has come from observational studies in Africa. The majority of these studies were carried out in disaster situations in which no alternative strategy was feasible. Extrapolating the results of those studies to India or other developing countries in non-emergency situations may not be appropriate (19). There is a need to generate more robust evidence on the applicability of home-based management in the Indian setting (20).

Methodological issues

Researchers planning to submit research proposals to the ICMR will have to carefully balance the scientific rigor of the study with the operational challenges of conducting the study in the community setting due to the inherent methodological issues, which are as follows:

Sample size

The prevalence of -3SD malnutrition (weight-for-height) in the community is already very low in India. The ICMR's eligibility criteria require the study subjects to be -3SD and the cases must be uncomplicated. This would make only a small sub-group of SAM children in the community eligible to participate in the study. However, as the prevalence of -3SD malnutrition is low; the required sample size for the study would be high. In addition, not all the subjects found eligible need consent to participate in the RCT, therefore reducing the actual sample size further when compared to the requirement. Therefore, after adjusting for such dropouts, the potential eligible subjects available in the community for inclusion may be just about one quarter of all SAM children. Therefore, the ICMR's insistence on community-based research makes the task extremely demanding, as the study cannot be done in one single community to fulfill the sample size. One would have to throw the net wide and increase the geographical spread of the study to achieve the required sample size.

Case definition of SAM

The diagnostic criteria proposed by UNICEF and WHO for the identification of SAM in children under five years of age are (i) weight-for-height below –3SD (SD or Z scores) of the median WHO growth reference; (ii) visible severe wasting; (iii) the presence of bipedal oedema; and (iv) a mid-upper arm circumference of below 115 mm (21). The WHO guidelines were modified by the Indian Academy of Paediatrics, which specified a weight-for-height/length below 70% NCHS median or ≤3SD that may be accompanied by visible wasting and bipedal oedema. Measurement of the circumference of the mid-upper arm could also be utilised (20).

Inclusion criteria

Case-finding and the diagnosis of SAM in the community constitute only the first step of the proposed study. All cases diagnosed even on the basis of the ICMR eligibility

criteria may still not qualify for recruitment in the study, since the diagnostic eligibility criteria would necessarily be accompanied by the operational eligibility criteria for participation in the research. Additional operational eligibility criteria for participation in the research will have to be built into the proposed study to ensure lower attrition. In addition to the criterion of the child being an uncomplicated case of SAM, other operational eligibility criteria that could be used on the basis of earlier studies (20) are: (i) the mother or caretaker is not employed full-time, (ii) the family lives within 5 km of a nutrition rehabilitation centre; (iii) the mother or caretaker can be trained to provide the child a home-based diet, and (iv) the family is financially able to provide the recommended home-based diet.

Follow-up issues

An intervention research study among SAM children would require repeated follow-ups, especially if it is a community-based study. On the basis of studies carried out in India (16), one could suggest that the frequency of the follow-up visits should preferably be: (i) 2 contacts a week, with a gap of at least 48 hours between the contacts in the first two weeks, (ii) once a week for 3–8 weeks, and (iii) every 4 weeks from 8 weeks to 16 weeks. During each visit, the child's dietary intake should be recorded by the recall method, and a detailed general physical and systemic examination should be conducted.

Endpoint

The objective outcome of the intervention study could be to achieve weight gain of more than 5 g/kg/d, which is the standard criterion for the effectiveness of an intervention for SAM children, as defined by WHO (22). The rehabilitation phase is considered to end when children attain −1SD (90%) weight-for-height. However, the feasibility of using this criterion in community-based programmes needs to be tested (23).

As suggested in a global review of SAM, published in *The Lancet* (1), an appropriate indicator of acute malnutrition (such as measurement of the mid-upper arm circumference) should be included as a standard element both of growth monitoring programmes and integrated management of childhood illness. This would allow these programmes to diagnose acute malnutrition more effectively. This indicator is essential if cases of SAM are to be detected early, before complications arise and while cheap outpatient treatment is possible. At present, growth monitoring programmes do not include any indicator of acute malnutrition and integrated management of childhood illness includes only "visible severe wasting", an indicator that is subjective, difficult to use in practice and unreliable. Measurement of the circumference of the mid-upper arm is easy to perform and is efficient in identifying children who need specialist interventions. Without this, most cases of SAM will go undiagnosed and untreated.

Operational and logistical issues

A community-based study of SAM will involve tremendous operational challenges. Home-based management does not necessarily mean that SAM children do not require any skilled care at home. It is extremely important to note that short-term therapeutic nutrition for 6–8 weeks is an integral component of home-based management of SAM (2).

The need for close monitoring and supervision

Experience and evidence from earlier studies have shown that in the absence of external support and home visits, the outcomes of home-based management of SAM children are not effective, even in research settings. It has been clearly demonstrated that home-based management using food prepared at home and involving hospital-based follow-up is associated with a sub-optimal and slow recovery (16). In a community-based study, it would become difficult to monitor compliance with the therapeutic diet as the SAM children would be scattered across a wide geographical region spanning several kilometers. This would be compounded by the fact that the proposed study period is six months,. Even if hypothetically, such a study came out with a prescriptive therapeutic food, a health economics study would have to be undertaken to estimate its cost-effectiveness and culturally acceptability. Spreading the community study across a large geographical area would prove to be a disadvantage in this respect as well. The prescriptive therapeutic food suggested by the RCT in one state may not be culturally acceptable in other states as there is a large variation in food habits even within the same state.

Ethical issues

As per the WHO guidelines, SAM children should be treated in hospital. However, home-based management is being promoted due to economic and other resource constraints. Following the same principles, RCTs on the medical management of SAM children are best carried out in facility-based settings, eg hospitals. This allows researchers to monitor the child's compliance with the therapeutic diet suggested by them, a process aided by supervision by motivated staff members who are in touch with the child on a daily basis. In a community-based intervention study spanning six months and a large region, it would be impossible to ensure compliance of the study and control children with the therapeutic food.

The choice of control

Several classical options for the selection of controls have been exercised by various SAM trials, ranging from the provision of no intervention to that of an alternative intervention, such as home-based dietary management or facility-based standard treatment.

In a conventional RCT, there is normally no manipulation of the control arm, which is also not required to be monitored for any type of compliance with any component of the research study. Generally, only the study group is administered the

new intervention and its compliance with the intervention is constantly monitored. However, for ethical reasons, it is not permissible to exercise the option of administering no intervention to the control group. Considering that SAM children have special needs, it is not fair to place some such children in a control group and deny them the therapeutic intervention. The children in the control group are equally in need of the special professional nursing and medical care provided to the children in the treatment group. Unlike other RCTs, trials on SAM would require the administration of two varieties of therapeutic food – new therapeutic food to the study group and conventional therapeutic food to the control group. In keeping with the ideal qualities of therapeutic food proposed by WHO, the new therapeutic food (i) should not need to be prepared in any form before consumption, (ii) should resist microbial contamination, and (iii) can be stored at ambient temperature (19).

Intervention among control group must be mandatory

The validity of the data generated by an unsupervised community-based nutritional intervention study would be dubious. A review of the evidence shows that any research on the home-based management of SAM requires an intervention in the control group. In earlier studies which demonstrated the effectiveness of home-based management, even without the provision of ready-to-use therapeutic food (RUTF) or any other food, a considerable effort had to be made to educate the mothers (19). It would be necessary to instruct mothers and carers on feeding the child and health promotion. It has been demonstrated clearly that carers are more likely to follow advice on what to feed the child, how much to feed and the frequency of feeding if they first practise what to do under supervision (23).

Any community-based trial on malnutrition must be all-inclusive

In the proposed ICMR research, moderately malnourished children have been left out due to the exclusion criteria. Such children will, therefore, not be eligible to receive the research study's interventions. The ICMR has explicitly stated that the motives for excluding moderately malnourished children are to keep the sample size small and reduce the cost of the study. This raises ethical concerns – can moderately malnourished children who are in need of intervention be left out of any intervention that is directed at treating malnutrition?

The researchers are bound to come across moderately malnourished children as a byproduct of the screening process. One should follow ethical standards and feed them as part of the research project with some therapeutic food or the other, whether it is the intervention food or the control food. When working out the financial details of the study, one needs to take into account the cost of feeding almost 40% of the children in the community within the study area. It would be unethical to intervene only in cases of SAM children because they are few in number, and ignore the mildly and moderately malnourished children just because they are in huge numbers.

RCTs may not be appropriate for community-based SAM intervention studies

There is a need to review how far RCTs focusing exclusively on SAM children are appropriate for achieving the ICMR's objectives. RCTs are highly protocol-driven research studies that require intense monitoring and follow-up of the study subjects. This makes these studies very costly. These factors go against the very spirit and purpose of home-based management strategies. It is important to bear in mind that home-based management was conceived of and designed especially for implementation in areas where the health infrastructure is poor or nonexistent, and where monitoring and supervision may not be feasible. This is one of the main reasons for which home-based management very often results in only a transient improvement in the child's condition: the deprivation at home causes a relapse (16).

There is no point carrying out RCTs in India without addressing the factors that have led to their failure earlier. It is a foregone conclusion that the logistical support provided during RCTs cannot be replicated under natural conditions in a community-based programme. This explains why interventions that have proven effective under the study conditions of RCTs have very often turned out to be ineffective under field conditions. The intensity of monitoring and supervision cannot be sustained in community-based programmes (24, 25). A global review of studies on SAM children (1) has shown that many of the home-based management programmes failed to yield positive results and the relapse rate was relatively high.

Conclusions and recommendations

It would be ethically wrong to conduct another RCT on SAM children without adequately addressing the well-documented reasons for the failure of home-based management of these children. Some of the main reasons are as follows: (i) the children, both in the study and control arms, are not provided with an adequate supply of therapeutic food; (ii) the minimum number of weekly home visits are not made; (iii) there is no predetermined monitoring mechanism; and (iv) funding and the external provision of food are not continued during and after the study period. The research protocol of the new study should explicitly mention its strategies to address each of the above components.

The proposed RCT study should ideally be carried out in three stages, as follows.

Stage I

The first stage could consist of a facility-based RCT, which would be best suited to answer the primary research question on the relative efficacy and cost-effectiveness of the proposed new therapeutic food for SAM children. As suggested by Ashworth, facility-based RCT is always preferable since the researchers have a minimum degree of control over data collection and monitoring (23). A facility-based study need not require the SAM children to be admitted in hospital, eg a child could be referred to a nutrition centre initially and visit it

daily. After 1–2 weeks of very rapid growth, and once the carer has learnt the requisite skills and gained the confidence to achieve catch-up growth at home, the child could be referred for home-based rehabilitation. At this stage, the child would be required to make three weekly visits to the centre, where he/she would be weighed and his/her progress assessed.

Stage II

The second stage could consist of a community intervention study, which would identify two communities with identical levels of malnourishment of all three grades. In one community, children with malnourishment of all grades could be given the new therapeutic food. Malnourished children belonging to the second community, which would serve as the control community, would be put on standard therapeutic food. There would be no blinding or randomisation in either community. The mean weight gain among the malnourished children could be the indicator of the final outcome.

Stage III

In the final stage, a qualitative study employing anthropological methods could be carried out as it would be the best suited for evaluating the secondary outcomes of the proposed ICMR study, ie cultural acceptability and feasibility.

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