Safety of using mid-upper arm circumference as a discharge criterion in community-based management of severe acute malnutrition in children aged between 6 and 59 months

Study Protocol

1. Objectives

- Evaluate the safety of using mid-upper-arm-circumference (MUAC) as a discharge criterion in community-based management of severe acute malnutrition (SAM) in children aged between 6 and 59 months.

- Describe the length of stay when MUAC is used for both admission and discharge in community-based management of SAM in children aged between 6 and 59 months.

2. Background

Study rationale

The use of MUAC as a *general* tool (i.e. for case-finding, referral, admission, monitoring and discharge) has the potential to allow community-based management of acute malnutrition (CMAM) services to be delivered within the Integrated Management of Childhood Illness (IMCI) framework at peripheral health facilities, within community health worker / health extension worker programs and growth monitoring and promotion programs, in resource-scarce settings, and in other settings where the use of weight-for-height (W/H) is problematic.

In May 2007, the use of MUAC for case-finding, referral, and admission to CMAM services was accepted by the World Health Organisation (WHO), the World Food Program (WFP), the United Nations Standing Committee on Nutrition (UN/SCN), and the United Nations Children's Fund (UNICEF). MUAC is now widely used in CMAM programs for these purposes.

In May 2009, the use of proportional weight gain (i.e. 15% or 20% weight gain) as a discharge criteria was endorsed by WHO and UNICEF with the intention of removing the need for height measurement and avoiding the problem of children simultaneously meeting both MUAC admission criteria and W/H discharge criteria. Unintended and negative consequences of the use of proportional weight gain as a discharge criteria are:

- The most wasted children tend to receive a shorter period of treatment than less wasted children when it is appropriate that they receive a longer period of treatment.

- Some of the least wasted children may require a very long period of treatment to meet the proportional weight gain discharge criteria.

These problems were clearly demonstrated in data presented by Médicins Sans Frontières (MSF) at the MM2 meeting in Geneva in February 2010. The use of MUAC in both admission and discharge criteria for CMAM programs may address this problem.

In 2008, data from a Save the Children-US CMAM program in Ethiopia were analysed to compare MUAC gain and weight gain in SAM children receiving treatment in outpatient therapeutic care (OTP). This work showed that MUAC and weight respond similarly to treatment. This finding, presented at the CMAM workshop in Washington DC in April 2008 and independently confirmed by MSF in 2010, suggests that it may be safe to use MUAC for both monitoring and discharge in CMAM programs.

The Save the Children-US data were also analysed with respect to the expected length of stay of patients in a program using MUAC for both admission and discharge. This analysis, also presented at the CMAM workshop in Washington DC in April 2008, suggests that the average length of stay within such a program will be similar to that observed in programs using discharge criteria based on either W/H thresholds or proportional weight gain.

The proposed study will:

- Investigate whether MUAC may be safely used as a program discharge criterion.
- Describe the length of stay of patients in a CMAM program using MUAC for both admission and discharge.
- Investigate whether using MUAC for both admission and discharge addresses the problem of inappropriate duration of treatment episodes for the most severely wasted cases and the least severely wasted cases which is associated with the use of proportional weight gain as a discharge criteria.

The proposed study will also further describe the relationship between gain in MUAC and gain in weight during treatment. This will inform future work on the development and testing of MUAC-based tools for monitoring response to treatment.

3. Plan of investigation

Study hypotheses

- Discharge from outpatient care for children aged between 6 and 59 months with SAM based on a threshold of MUAC ≥ 125 mm is safe: In the three months following discharge, less than 10% of children will experience a negative outcome of relapse to program admission criteria or non-accidental, non-violent death. Accidental deaths and deaths due to violence will not be classified as a negative outcome for the purpose of this study.

- The average length of stay within a program treating children aged between 6 and 59 months with SAM and discharging using a threshold of MUAC ≥ 125 mm is similar to that observed in programs using discharge criteria based on either W/H thresholds or proportional weight gain.

- The use of MUAC for both admission and discharge addresses the problem of inappropriate duration of treatment episodes associated with the use of proportional weight gain as a discharge criteria.

Study design

This is a *standards-based trial* in which a maximum level (the *standard*, 10%) for the proportion of program beneficiaries who relapse or die from non-accidental, non-violent causes within three months of discharge is established, and a check is made to confirm that this standard is not exceeded.

The 10% standard is taken from the three-fold criteria of success for community-based treatment of severe malnutrition (i.e. case fatality rates below 5%, mean weight gains at or above 5g / kg / day, and relapse / readmission rates below 10%) presented in:

> Ashworth A, *Efficacy and effectiveness of community-based treatment of severe malnutrition*, Food and Nutrition Bulletin, 2006;27(S):S24–S48
>
> Collins S, Sadler K, Dent N, Khara T, Guerrero S, Myatt M, Saboya M, Walsh A, *Key issues in the success of community-based management of severe malnutrition*, Food and Nutrition Bulletin, 2006;27(3):S49-S79

A standards-based trial is simpler, cheaper, and faster than a *comparative trial* since randomisation of subjects and treatment sites is not required, and sample size requirements are smaller.

A comparative trial would need to be an *equivalence trial* and such trials usually require large sample sizes. The standards-based approach should allow trials to be undertaken at multiple sites for the same cost as a single comparative trial. The lower sample size requirement means that trials may be feasible in developmental settings where patient numbers are likely to be low compared to emergency settings.

The intention is to create and test a protocol that could be easily replicated with low levels of supervision in order to establish a multi-centre evidence base within a few years. Furthermore a set of several small datasets from diverse locations would represent a stronger evidence base than a single large dataset from a single location.

Eligibility

The study will take place in a program using MUAC for case-finding, referral and admission. The SAM definition (and study eligibility criterion) used in the study will be:

MUAC < 115 mm

in children aged between 6 and 59 months. Children presenting with bilateral pitting oedema but with MUAC ≥ 115 mm will be admitted to the program for treatment but will not be enrolled in the study. This is because patients admitted with bilateral pitting oedema with MUAC ≥ 115 mm are discharged using criteria based upon loss of oedema and length of stay in program.

Subjects will be recruited sequentially from admissions in the study location. Study admission criteria will be MUAC < 115 mm in children aged between 6 and 59 months. For the purpose of investigating the safety of using MUAC as a program discharge criteria, subjects will start to contribute data when they are discharged as cured based on MUAC discharge criteria. For the purposes of investigating length of stay, subjects will contribute data as soon as they are admitted to the program.

Children identified by the program with MUAC < 115 mm but with complications requiring inpatient care will be enrolled into the study. For the purposes of investigating length of stay, these subjects will contribute data as soon as they are identified by the program (i.e. time spent in inpatient care will contribute to a subject's lengths of stay).

Methods

Upon admission, program staff will record the date of admission, the age, sex, MUAC, triceps skinfold, and weight of the child, a medical history, and the results of a physical examination which will include an appetite test for the ready-to-use therapeutic food (RUTF) used by the program. Information required for post-discharge follow-up and defaulter-tracing will also be collected at this time.

During treatment, program staff will record MUAC, triceps skin fold, and weight, test appetite, check for IMCI danger signs and other clinical signs based on the Action Protocol for Outpatient Care at each visit throughout the treatment episode. Any subject who fails to gain weight or develops medical complications in line with the Action Protocol for Outpatient Care will receive a home visit and, if indicated, be referred to inpatient care for investigation and treatment. Program staff will record all adverse events and the date of the event upon its occurrence.

Adverse events include death, treatment failure (e.g. failure to respond to treatment, deterioration of condition, referral to inpatient care, and referral for medical investigation based on the Action Protocol for Outpatient Care), and defaulting (reason for defaulting will be sought). All reasonable efforts will be made to find and re-admit defaulting cases.

Subjects will be discharged from the program when their MUAC is greater than or equal to 125 mm at two consecutive clinic visits and they are clinically well and alert.

At discharge program staff will record the date, MUAC, triceps skinfold, weight, and stature of the child (length for children less than two years old and height for children two years old and above). Caregivers of subjects will be given a 14-day supply of ready-to-use therapeutic food (RUTF). Caregivers will be informed to return to the program if the subject's condition deteriorates. All subjects returning to the program after discharge who meet program admission criteria will be readmitted to the program. All subjects returning to the program after discharge who do not meet program admission criteria will be advised to return to the program if the subject's condition deteriorates and, if necessary, referred to appropriate clinical services.

After discharge an appropriately qualified healthcare provider will visit subjects in their own homes every two weeks for a period of three months. At each home visit, the healthcare provider will record the date, MUAC, triceps skinfold, and the weight of the child. S/he will also assess the general health of the subject, the subject's appetite, check for the presence of bilateral pitting oedema, and check that the subject is clinically well and alert. Any subject meeting program admission criteria at the home visit will be referred for re-admission. Caregivers of all subjects not meeting program admission criteria will be informed at each home visit to return to the program if the subject's condition deteriorates. Any subject judged to be in need of medical attention will be referred to the appropriate clinical service.

Outcomes

A negative outcome (relapse or death) will be recorded for a subject if:

- The subject returns to the program and is found to meet the program admission criteria at any time during the three-month follow-up period (passive follow-up).
- The subject is found to meet program admission criteria after discharge by health staff during a follow-up visit at any time during the three-month follow-up period (active follow-up).
- The subject is reported as having died from non-accidental, non-violent causes at any time within the three-month follow-up period.

Subjects readmitted to the program after discharge will be re-enrolled in the study if the study admission criteria are met. These subjects will be recorded as *readmitted cases* so that readmission into the program may be accounted for during data analysis.

Losses during the three-month follow-up period will be recorded and the reason sought (e.g. from a neighbour, community leader, or other informant).

Study duration

The data-collection phase of the study is expected to last approximately 17 months. Study enrolment will be carried out for a 12 month period, with treatment lasting approximately 8 weeks for each child admitted to the program. After discharge each child will be followed for a period of 3 months to assess whether the child experiences a negative outcome.

Research location

The study site will need to be an outpatient therapeutic care program in which good quality services and follow-up of children after discharge from the program can be assured. Support provided by an experienced Valid International Ltd. CTC advisor will aim to ensure and maintain program quality. The study site will use current best-practice protocols and methods for community-based management of SAM. The choice of location will be based on opportunities that arise that would be suitable but, if possible, will be with a USAID / Office of US Foreign Disaster Assistance or other USAID-funded program (this is a stated preference of AED/FANTA-2).

Sample size

A time-limited approach will be used to determine the number of subjects that are enrolled in the study.

To control for potential seasonal effects, study enrolment period will be a single twelve month period. This is the shortest enrolment period required for this study. All children who meet the study admission criteria during the defined enrolment period will be enrolled in the study. Study enrolment will occur only during the defined enrolment period.

From reviews of NGO-implemented and district-level CTC programs meeting SPHERE minimum standards for coverage, it is anticipated that approximately 500 children will be recruited during the defined enrolment period. This anticipated *sample size* is sufficient for the proposed primary analyses:

Analysis	Expected precision
Proportion of discharges relapsed or died three months after discharge	better than ± 3%
Median duration of treatment episode	better than ± 2 days
Relationship between admission MUAC and weight gain achieved at discharge	not known

During the period of the study Valid International Ltd. will provide support to the program to improve and maintain program recruitment and coverage based on finding of ongoing investigations using the SQUEAC methodology. This is to ensure that the program and, hence, the study recruits a representative cross-section of children aged between 6 and 59 months with SAM, as well as ensuring that the study achieves a useful sample size.

Analysis

Primary analyses

The primary analyses for this study are:

- To assess whether the standard of ≤ 10% of planned discharges relapsed or died during the three months after discharge has been met. This analysis will be undertaken by reporting the proportion of children that have relapsed or died during the study period.

- To assess the cost and workload implications of adopting the MUAC ≥ 125 mm discharge criterion. This analysis will include a descriptive analysis of length of treatment episode for comparison with already available data from programs using discharge criteria based on either W/H thresholds or proportional weight gain.

- An analysis of relationship between admission MUAC and weight gain achieved at discharge in order to ascertain whether the use of MUAC for both admission and discharge addresses the problem of inappropriate duration of treatment episodes associated with the use of proportional weight gain as a discharge criteria.

Analysis

Additional analyses

A number of additional analyses will be performed:

- Comparison of MUAC ≥ 125 mm and other discharge criteria at time of discharge:
    - Proportion of subjects with MUAC ≥ 125 mm having achieved ≥ 15%, ≥ 18% and ≥ 20% proportional weight gain at the close of the treatment episode.
    - Proportion of subjects with MUAC ≥ 125 mm having achieved WHZ ≥ -2, WHZ ≥ -1.5, WHZ ≥ -1, WHM ≥ 80%, WHM ≥ 85%, and WHM ≥ 90% at the close of the treatment episode. Both NCHS and WGS references will be used for this analysis.
    - Distribution of WHZ and WHM in subjects with MUAC ≥ 125 mm at the close of the treatment episode. Both NCHS and WGS references will be used for this analysis.
- An analysis of outcomes to investigate whether adverse outcomes are associated with weight gained during the treatment episode or W/H at discharge.
- An analysis of patterns of weight gain and MUAC gain during the treatment episode and after discharge. The primary aim of this analysis is to inform the design of monitoring instruments. Interim analyses will be performed during the study, and candidate monitoring instruments designed and tested. It is expected that one or more candidate monitoring tools will be available for further testing at the end of this study.
- An analysis of triceps skinfold thickness, MUAC, mid-upper arm muscle area, and mid-upper arm fat area. Triceps skinfold is a measure of the quantity of fat in the upper arm. Together with MUAC, it is used to estimate the quantity of muscle and the quantity of fat in the upper arm. Repeated measurement of triceps skinfold and MUAC will allow changes in the relative proportions of fat and lean mass in each treated case to be plotted over the duration of the treatment episode and post discharge follow-up period. If, for example, it is observed that during treatment and at some point below MUAC = 125 mm, cases gain fat mass without gaining lean mass then a lower MUAC discharge threshold may be safe and, by shortening the length of the treatment episode, allow some resource savings. This analysis may also inform the design of monitoring instruments. An analysis of outcomes to investigate whether adverse outcomes are associated with lean mass gained during the treatment episode will also be undertaken.

Summary of study outcomes

Primary outcome(s)

This study will:

- Allow the investigators to conclude whether or not the standard of ≤ 10% relapse or death three months after discharge was met when a discharge criterion of MUAC ≥ 125 mm was adopted.

- Allow investigators to predict the cost and workload implications of adopting the MUAC ≥ 125 mm discharge criterion

Secondary outcome(s)

The study will:

- Provide information on the proportion of children who, by the time they had attained a MUAC ≥ 125 mm, also attained historical discharge criteria

- Provide data to inform decisions regarding the feasibility of using MUAC-based patient monitoring tools and, if appropriate, provide candidate tools for further testing.

Study limitations

This study will evaluate the proportion of relapses and deaths that occur among children treated for SAM with the CTC / OTP protocol using a discharge criterion of MUAC ≥ 125 mm in the program site selected for the study. Additional studies may be needed to assess whether a discharge criterion of MUAC ≥ 125 mm is safe in other CMAM programs and geographic settings. The intention is to create and test a protocol that could be easily replicated with low levels of supervision in order to establish a multi-centre evidence base in the medium term.

The analyses carried out with this study design will not be able to demonstrate that alternative discharge criteria would have resulted in fewer negative outcomes than a discharge criterion of MUAC ≥ 125 mm. A comparative study with multiple sites using different discharge criteria is required for such an analysis.

Funding position

This study is fully funded (US$211,008.00) by the Academy for Educational Development (AED) Food and Nutrition Technical Assistance II Project (FANTA-2) as project 4001-08-1-01 / 4001-VALID-00 / Task Order 4.

Regulatory and ethical considerations

The study will comply fully with the World Medical Association Declaration of Helsinki regarding ethical principles for medical research involving human subjects.

Potential risks

The principal risk associated with this study is that the 125 mm MUAC threshold results in premature discharge and an unacceptably large number of children relapse or die after discharge.

The MUAC discharge threshold of 125 mm selected for this study has been selected with consideration of patient safety. Studies of relapse in CTC programs indicate that discharge with MUAC < 125 mm regardless of W/H is associated with relapse in both HIV positive and HIV negative patients. Historical cohort studies from many settings consistently show that the risk of near term mortality in untreated children at or about the MUAC = 125 mm threshold is not elevated above local baselines. The 125 mm threshold has been used for many years as the case-defining threshold for moderate acute undernutrition (i.e. children with MUAC ≥ 125 mm are not usually considered to be significantly undernourished).

In order to minimise risk, subjects will only be discharged from the program when their MUAC is greater than or equal to 125 mm at two consecutive clinic visits and they are clinically well and alert. Caregivers will be given a 14-day supply of RUTF on discharge and will be informed to return to the program if the subject's condition deteriorates. In addition, an appropriately qualified healthcare provider will visit subjects in their own homes every two weeks for a period of three months after discharge and any subject meeting program admission criteria at a home visit will be referred for re-admission. In order to further minimise risk an interim analysis will be performed six months after the start of the study in order to ascertain whether the following study stopping rule applies:

> Six months after study enrolment is initiated, the data collected on study subjects who have completed the three month follow up period will be analysed. If the proportion of children who have experienced relapse or death due to non-accidental, non violent causes is ≥ 20%, the study will be stopped due to concerns about the safety of a MUAC discharge criterion of ≥ 125mm.

The funding body for this study (AED/FANTA-2) has stated:

> *While it is not anticipated that this situation* [i.e. application of the study stopping rule] *would occur, if the 20% threshold were to be reached within six months of initiating study enrolment, the study would <u>not</u> be permanently terminated. Instead, AED/FANTA-2 will request that a higher discharge criterion be evaluated (≥130 mm) and that the 12 month study enrolment period begin anew. All other study protocols would remain consistent for this conditional new phase of the study. Should this situation occur, a revised budget would be prepared and a modification to this task order* [i.e. the funding agreement] *executed.*

Potential benefits

The ability of CMAM programs to admit and discharge SAM cases using MUAC will allow further decentralisation of CMAM services into community health worker, health extensions, and growth monitoring and promotion programs and may improve the coverage of existing programs.

We believe the risk-benefit ratio of this study is positive

Informed consent

Informed consent will be sought from caregivers of subjects.

Payment to subjects and their families

There will be no payment to subjects or their families for participation in this study.

Confidentiality

Data handling procedures and data protections will correspond to the requirements of the UK Data Protection Act 1998, the UK Venereal Diseases Act 1917, and the UK Venereal Diseases Regulations of 1974 and 1992.

4. Study team

The study will be carried out by Valid International Ltd. and a major international NGO. An experienced CTC Advisor will support the set-up of the program within which the study will be implemented and a full time international study supervisor with a national counterpart will be based at the study site to conduct the day to day implementation and monitoring of the study. In addition to the usual programs staff 50 community health workers will be incentivised to conduct the follow-up of subjects and assist in defaulter tracing during the study.

5. Activities

The study will be carried out over a 24 month period according to the project timeline below: