Taimaka CMAM – SAM trial

Manual of Operations and Procedures

Trial registration: NCT05473234

TABLE OF CONTENTS

ABBREVIATIONS

CHW: Community Health Worker
CMAM: Community management of acute malnutrition
DSMC: Data and Safety Monitoring Committee
HAZ: height-for-age z-score
IRB: Institutional Review Board
MUAC: mid-upper arm circumference
ODK: open data kit
OTP: outpatient therapeutic program
RDT: rapid diagnostic test
RUTF: ready-to-use therapeutic food
SAM: severe acute malnutrition
SD: standard deviation
SES: socio-economic status
UCSF: University of California San Francisco
WAZ: weight-for-age z-score
WHO: World Health Organization
WHZ: weight-for-height z-score

1. INTRODUCTION

1.1 Background and Rationale

Severe acute malnutrition (SAM) affects nearly 19 million children under the age of 5 annually.[1] Current World Health Organization (WHO) guidelines for treatment of SAM include outpatient treatment with ready-to-use therapeutic food (RUTF). Children with SAM often bear a large burden of infectious disease, have 9 times the risk of all-cause mortality compared to their well-nourished peers, and face a stronger risk of infectious mortality.[2,3] Because malnutrition can suppress the immune system, children with SAM and co-existing infection are often asymptomatic. As a result, the WHO has recommended that the routine treatment of children with SAM include a broad-spectrum antibiotic. However, the evidence base for this recommendation is minimal. Two studies of amoxicillin as adjunctive therapy for SAM found mixed results.[4,5] In Malawi, routine amoxicillin led to increased nutritional recovery and decreased mortality.[4] In Niger, there was no effect of routine amoxicillin on either nutritional recovery or mortality.[5] Importantly, a majority of the children included in the Malawi study had kwashiorkor, whereas children with kwashiorkor were excluded in Niger. A pooled analysis of the two studies found no benefit of amoxicillin for recovery.[6] A third study of daily co-trimoxazole for complicated SAM additionally found no benefit for nutritional recovery or mortality.[7] The role of antibiotics for mortality and nutritional recovery among children with uncomplicated severe acute malnutrition remains unclear.

A recent cluster-randomized trial demonstrated that mass azithromycin distribution reduces all-cause mortality at the community level.[8] In Niger, Tanzania, and Malawi, mortality was reduced by nearly 14% in communities randomized to biannual mass single-dose azithromycin distribution to children 1-59 months in the MORDOR trial (*Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance*). The largest effects were seen in Niger, with nearly 1 in 5 deaths averted, and in children less than 6 months of age, with approximately 25% reduction in mortality.

Azithromycin as adjunctive therapy may offer several advantages over amoxicillin or co-trimoxazole. First, a single dose of azithromycin has a long half-life, and thus dosing could occur during outpatient follow-up visits and would not rely on caregiver dosing. Second, amoxicillin and co-trimoxazole are much more commonly used for routine treatment in many regions of sub-Saharan Africa than macrolides, and baseline resistance to these antibiotic classes tend to be much higher.[9] Adjunctive therapy with azithromycin may be preferable, given overall reduced exposure compared to other classes.[10] Third, evidence from the MORDOR study in Niger indicated a substantial reduction in mortality with the use of a single dose of azithromycin in children without established infection. Given that children with uncomplicated SAM by definition do not have an established infection, the rationale for antibiotic use may be similar for that among children in the general population who are receiving presumptive treatment. As children with malnutrition are at particularly high risk of mortality, this subgroup of the population may stand to see greater benefits from a similar antibiotic regimen that has been shown to be efficacious in the general population.

1.2 Design Overview

We propose a randomized controlled trial to examine the effect of the adjunctive administration of azithromycin compared to amoxicillin in the treatment of children aged 6-59 months with uncomplicated SAM. We will randomize children presenting to nutritional programs in Gombe State, Nigeria to a single dose of oral azithromycin or a short course of oral amoxicillin upon admission into the program and follow them at each weekly clinic follow-up visit up to 8 weeks following admission. All enrolled children will receive non-antibiotic routine care for uncomplicated SAM as stated by the Nigeria guidelines, which includes ready-to-use therapeutic food (RUTF). Anthropometric and vital status data will be collected during follow-up. Weight gain and nutritional recovery over the 8-week study period will be compared by study arm.

1.3 Objectives

SPECIFIC AIM 1: Determine the effect of azithromycin on weight gain among children with uncomplicated SAM. *We hypothesize that children randomized to receive azithromycin will experience greater weight gain over an 8-week period compared to those receiving amoxicillin.*

SPECIFIC AIM 2: Determine the effect of azithromycin on nutritional recovery in children with uncomplicated SAM. *We hypothesize that children randomized to receive azithromycin will have increased nutritional recovery 8 weeks after admission to the nutritional program compared to children receiving amoxicillin.*

2. STUDY DESIGN

This randomized controlled trial is designed to determine the effect of administration of azithromycin compared to amoxicillin as part of the treatment of uncomplicated SAM in children aged 6-59 months on weight gain and nutritional recovery. We will randomize children presenting to Taimaka-run nutritional programs at health centers in Gombe State, Nigeria to a single dose of oral azithromycin or a short course of oral amoxicillin upon admission into the program. Apart from the administration of antibiotics, all children will receive standard outpatient treatment for uncomplicated SAM as specified in the guidelines of the government of Nigeria, which includes therapeutic feeding with RUTF. Enrolled children will be followed weekly at each routine clinic follow-up visit up until nutritional recovery. All enrolled children will return for a final study visit at 8 weeks following enrollment. Anthropometric and vital status data will be collected at each follow-up visit. Weight gain and nutritional recovery over the 8-week study period will be compared by arm as a primary outcome and at 12 weeks as a secondary outcome.

2.1 Study Setting

The trial will be conducted at outpatient therapeutic program (OTP) centers in Gombe State, Nigeria, which are run out of government-run primary healthcare centers (PHC) that Taimaka partners with for their CMAM program. Taimaka's program uses these OTPs to run nutritional programs for children presenting with SAM. The PHCs are government-run, integrated health centers and are overseen by the Primary Healthcare Development Agency. Taimaka's program links these centers to secondary facilities for referrals in the case of complications. The secondary facilities function as inpatient treatment centers (ITPs) and are overseen by the Hospital Services Management Board and the Ministry of Health.

2.2 Recruitment and Eligibility Criteria

Recruitment

Taimaka-employed community mobilizers (CMs) screen children for SAM at least once a month in the villages within the catchment areas of the program PHCs. If they are screened positive for moderate acute malnutrition (MAM) or SAM, they are referred to an OTP center. CMs screen for MAM and SAM using a tape to measure mid-upper arm circumference (MUAC).

Each participating OTP center has nutrition staff (henceforth known as health agents) trained to enter data and conduct anthropometric measurements. All data is collected electronically on an ODK custom platform. The health agents at the OTP centers are trained regularly on malnutrition guidelines, data collection and anthropometric measurements

All children presenting to the OTP centers for malnutrition will be screened, and eligibility for enrollment in the trial will be determined by health agents trained for the study.

Eligibility criteria for enrollment sites

For Phase 1, the 3 Taimaka-run OTP centers in Gombe state that will be eligible for enrollment are located within 1) General Hospital Deba, 2) General Hospital Bajoga, and 3) General Hospital Billiri.

For Phase 2, the Taimaka-run OTP centers in Gombe state will be located in PHCs in wards in these local government areas (LGAs): Deba, Billiri, and Funakaye (Bajoga is a town within the Funakaye LGA).

Eligibility criteria for individuals

Eligible individuals are children aged 6-59 months with SAM who present to an eligible OTP center during the study period and meet all of the following criteria:

Inclusion criteria (all must be met):

- Age 6-59 months
- Weight-for-height z-score (WHZ) < -3 SD or mid-upper arm circumference (MUAC) < 115 mm
- Either (a) no oedema or (b) Nutritional edema Grade I and II
- Primary residence within catchment area of enrollment site
- Available for full 8-week study
- Sufficient appetite according to a feeding test with ready-to-use therapeutic food (RUTF)
- Appropriate written informed consent from at least one parent or guardian

Exclusion criteria (any excludes):

- Age < 6 months or > 59 months
- WHZ ≥ -3 SD or MUAC ≥ 115 mm
- Primary residence outside catchment area of enrollment site
- Not available for full 8-week study
- Presence of nutritional edema Grade III
- Admission to a nutritional program for the treatment of SAM in the 2 preceding weeks
- Antibiotic use in past 7 days
- Clinical complications requiring antibiotic treatment
- Clinical complications requiring inpatient treatment
- Congenital abnormality or chronic debilitating illness that would lead to predictable growth faltering or reduce likelihood of SAM treatment benefit (such as cerebral palsy, Down syndrome, congenital heart disease, cleft lip/palate, sickle cell disease etc)
- Allergy to macrolides/azalides
- Insufficient appetite according to a feeding test with ready-to-use therapeutic food (RUTF)
- Parent or guardian refuses to provide consent

2.3 Randomization and Masking

Children meeting inclusion criteria will be enrolled by a local health agent after consent from guardian is obtained. At enrollment, children will be assigned a study identification number. Enrolled children will then undergo a baseline assessment. The baseline assessment includes data collection on demographics and socioeconomic status as well as anthropometric assessments. After completion of the baseline assessment, children will be randomized to receive either (1) a single dose of directly observed oral azithromycin plus a 5-day course of placebo or (2) a 5-day course of oral amoxicillin.

The randomization sequence will be generated by the UCSF investigators using R (R Foundation for Statistical Programming, Vienna, Austria). Children will be randomized in a 1:1

fashion to a single dose of azithromycin with short course of placebo or a short course of oral amoxicillin. The randomization sequence will be linked to the study identification numbers and kept separately so outcomes assessors are not aware of the treatment allocation. When a child has been enrolled and has completed the baseline assessments, a different health agent will determine the allocation and will administer study medication indicated as described in Section 4.

To keep the allocation concealed, only the study nurse administering treatment will have access to the randomization allocations. The study nurse will treat the child in a private room without the outcome assessor present. For each enrolled child, the treatment administered will be recorded on the mobile data collection app not accessible by the outcome assessor.

Given the nature of the intervention, the personnel administering treatment will not be masked to treatment assignment. Participants will be masked to treatment assignment, as parents of the children given azithromycin will receive a placebo syrup to give their child. Outcome assessors will be masked to treatment assignment; this will be accomplished by assigning one health agent to administer treatment and a separate masked health agent to perform outcome assessments, including anthropometry, and vital status updates.

2.4 Interventions

Children will be randomized to receive a single directly observed dose of oral azithromycin plus placebo or a short course of oral amoxicillin. Azithromycin and the first dose of amoxicillin will be administered at the time of enrollment (see Section 4 for study medication details). Except for antibiotics, all children will receive standard outpatient treatment for uncomplicated SAM per the guidelines of the government of Nigeria, which includes RUTF (Plumpy'Nut, Nutriset) as follows:

Weight (in kg)	RUTF (paste)	
	Packets per day	Packets per week
3.5 - 3.9	1 ½	11
4 – 5.4	2	14
5.5 – 6.9	2 ½	18
7.0 – 8.4	3	21
8.5 – 9.4	3 ½	25
9.5 – 10.4	4	28
10.5 – 11.9	4 ½	32
> = 12	5	35

Standard treatment also includes:
- Weekly appetite test, MUAC, and weight measurement
- Weekly clinical examination
- Weekly health and nutrition education
- Weekly evaluation of RUTF consumption
- Home visit if needed
- Monthly height / length measurement

2.5 Outcomes

Primary Outcome
Weight gain over 8 weeks (Specific Aim 1). Weight will be measured at all follow-up time points and weight gain will be defined as grams per kilogram per day (g/kg/day).

Secondary Outcomes
Nutritional recovery by 8 weeks (Specific Aim 2). Nutritional recovery will be defined as a child having WHZ ≥ -2 on two consecutive visits and no acute complication or edema for the past 7

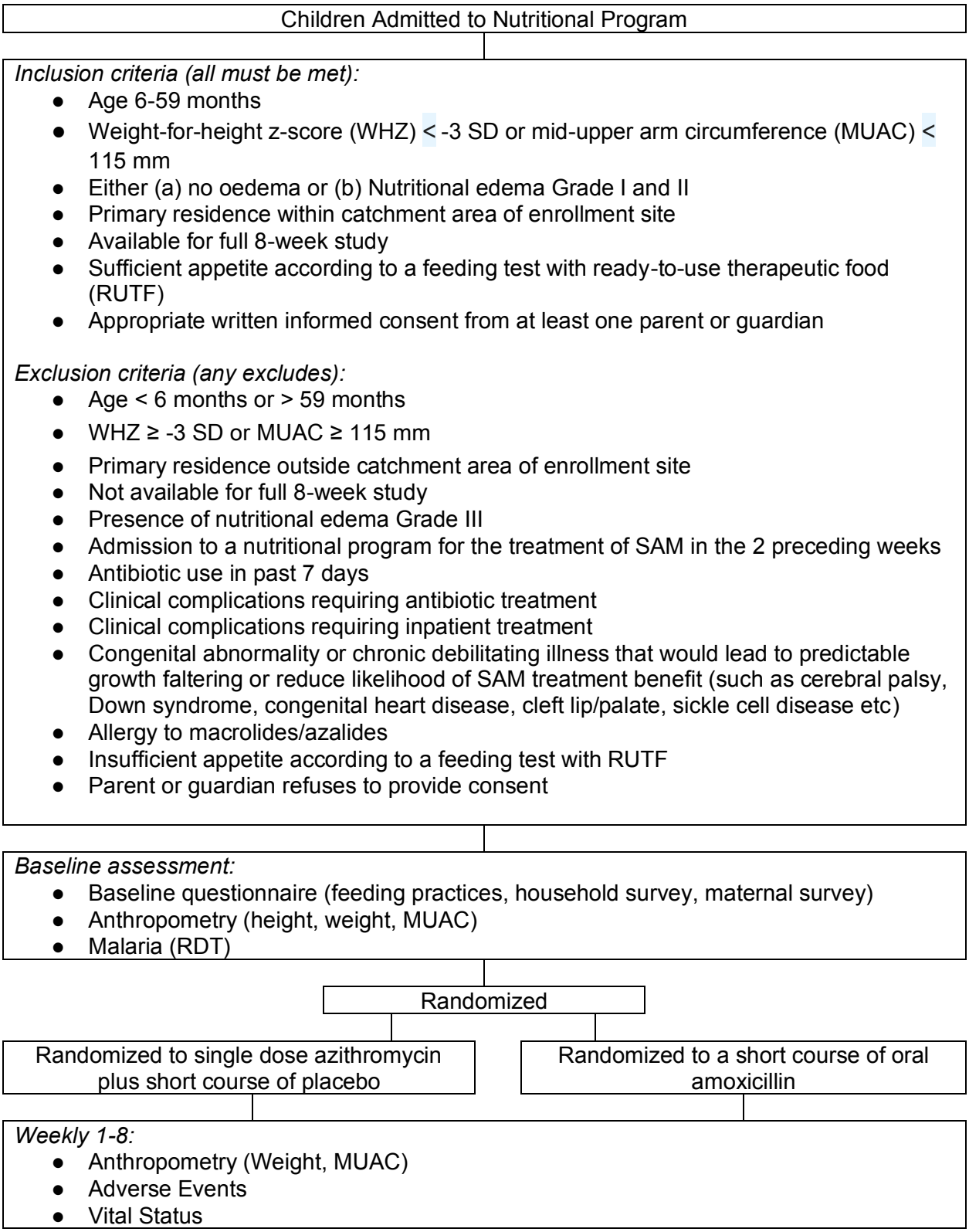
days AND / OR MUAC of ≥ 125mm on 2 consecutive visits and no acute complication or edema for the past 7 days. The criteria chosen to define the recovery will be the same one we used to admit the child into the program as defined in the national guidelines:

Criteria of admission	**Criteria of discharge**
MUAC < 11.5cm	MUAC > 12.5cm (for 2 consecutive weeks) Sustained weight gain Clinically well
Bilateral oedema	MUAC > 12.5cm No oedema for 2 consecutive visits Clinically well
WHZ < -3 SD	MUAC > 12.5cm AND WHZ >-2 for 2 consecutive visits Clinically well

- **Weight gain over 12 weeks.** Weight will be measured at all follow-up time points and at 12 weeks after admission to the program. Weight gain will be defined as grams per kilogram per day (g/kg/day).
- **Time to recovery.** Time from enrollment to nutritional recovery (defined above) will be calculated in days by subtracting the date of enrollment from the date of nutritional recovery.
- **Nonresponse at 8 weeks.** Nonresponse will be documented if a child does not meet the criteria for nutritional recovery at 8 weeks.
- **Transfer to inpatient care.** The occurrence, date, and reason for transfer from outpatient to inpatient treatment will be recorded.
- **Mortality by 8 weeks.** Vital status will be assessed at all follow-up time points and mortality will be defined as death during the study period. Date of death will be recorded.
- **Mortality by 12 weeks.** Vital status will be assessed at all follow-up time points and mortality will be defined as death during the study period. Date of death will be recorded.
- **Clinical signs of infection.** At all follow-up time points, clinical signs of infection will be recorded, including care-giver reported experience of fever, diarrhea, vomiting, and respiratory infection/cough and clinical diagnoses made at by site personnel
- **Adverse events.** Adverse events will be reported at all follow-up time points
- **HAZ.** Height or length will be measured monthly and height-for-age z-scores will be calculated.
- **MUAC.** Mid-upper arm circumference will be measured at all follow-up time points.
- **WAZ.** Weight will be measured at all follow-up time points and weight-for-age z-scores will be calculated.
- **WHZ.** Weight and height, assessed at all follow-up time points, will be used to calculate weight-for-height z-scores.
- **Malaria.** Rapid diagnostic tests for malaria will be conducted at baseline and week 8 to determine malaria infection status.

2.6 Participant Timeline

Figure 1. Participant Timeline and Flow



- Clinical examination outcomes (diagnoses, treatments)

Monthly:
- Anthropometry (Height, length)

Week 8:
- Malaria RDT

Week 12:
- Anthropometry (height, weight, MUAC)
- Vital Status

2.7 Study Team, Roles, Responsibilities

- **Investigators (UCSF)**. The UCSF investigators will be responsible for the overall study design and implementation, data management and monitoring, data analysis, and dissemination of results in collaboration with Taimaka investigators. The UCSF investigators will design and implement trainings for study procedures and maintain weekly communication with local Nigerian study staff.
- **Investigators (Taimaka Project).** The Taimaka investigators will be responsible for overall study design, implementation, data management and monitoring, data analysis, and dissemination of results in collaboration with UCSF investigators. The Taimaka investigators will oversee all local study activities, including training and regular supervision and monitoring of local study staff.
- **Medical Monitor.** The Medical Monitor will provide clinical oversight for the enrolled children. Study Team Members will report serious adverse events to the Medical Monitor within 24 hours of occurrence, and the Medical Monitor will determine whether or not the event is likely to be related to the study drug. In addition, the Medical Monitor will provide clinical guidance for the adverse event as needed.
- **Data and Safety Monitoring Committee.** The Data and Safety Monitoring Committee will provide independent oversight of data quality and patient safety during the course of the trial. See Section 8 for details.
- **Study Team Members (Taimaka project).** Study Team will be responsible for implementation of all study procedures as described in this protocol, including recruitment, consent, enrollment and randomization, drug administration, and collection of all study data.
    - **Health agent administering treatment.** A health agent at each OTP center will be trained to determine the randomization allocation of enrolled children and to administer azithromycin if indicated.
    - **Outcome Assessor.** One health agent will be an outcome assessor for each site and will be trained to manage consent, enrollment, and collection of all study data, including outcome assessments.

3. PROCEDURES

3.1 Training

All members of the OTP nutrition team will participate in multi-day training which will include a section on the particulars of study protocol. In addition, study nurses (study officers) who will be administering the treatment will receive a separate initial training. Study officers must achieve a score of >80% on the training quiz in order to participate in the study. Training will include a mix of lecture and practice. Taimaka's OTP manager will supervise the adherence to study protocol by the nutrition team and the study officer and regularly check up on their understanding and memory of study protocols.

3.2 Anthropometry

Anthropometric assessments (height or length, weight, and MUAC) will be recorded by health agents at baseline, weekly until recovery, week 8 and week 12.

Supplies

- Mobile data collection device & accessories
- Height and length tapes
- Digital scale
- MUAC strips
- Chucks and alcohol swabs
- Pens and sharpie markers
- Trash bags
- Extra set of AA batteries (6)

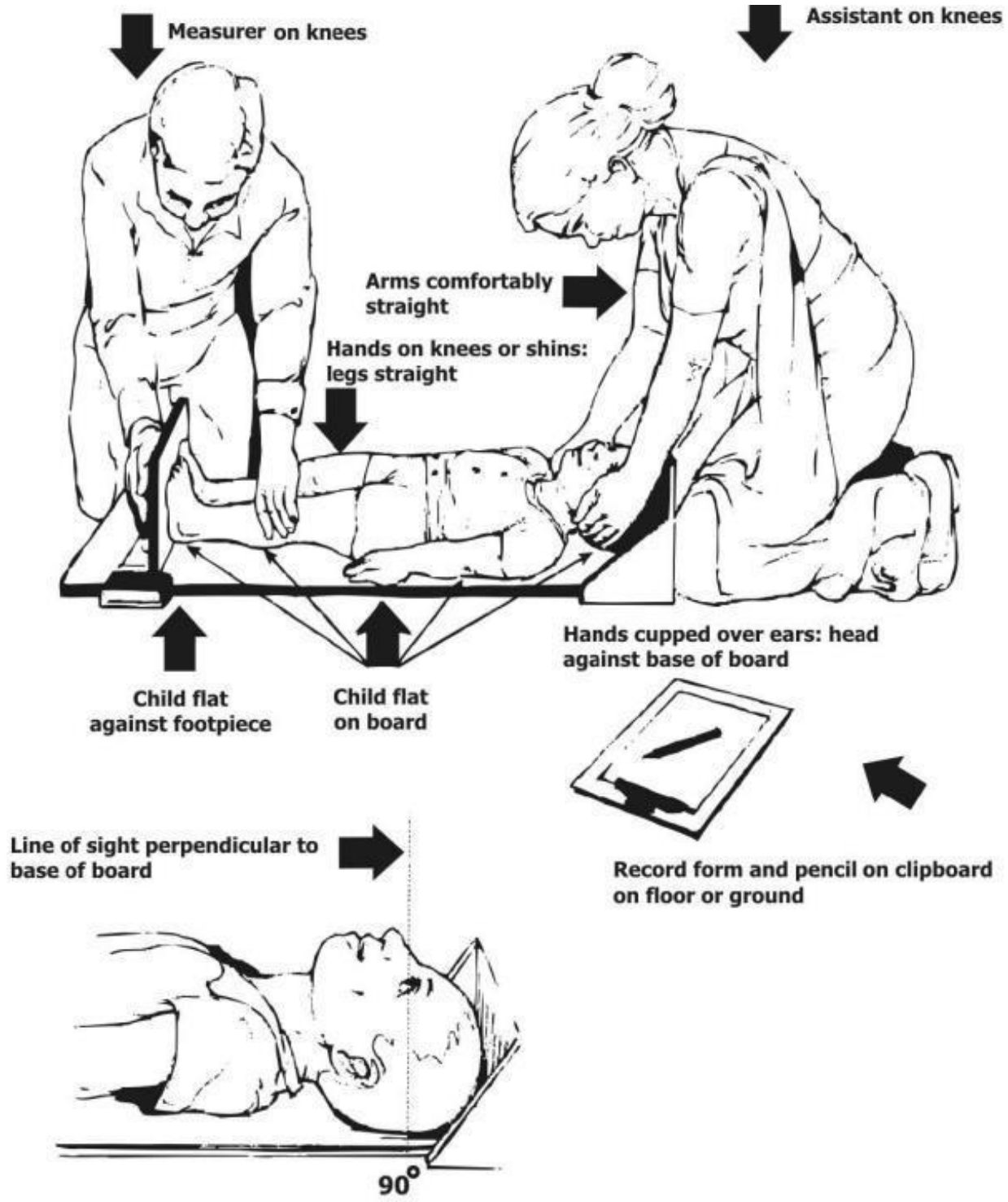
Anthropometry Team

Two health agents will conduct anthropometry: 1) examiner and 2) recorder. The examiner will conduct the anthropometric assessments, and the recorder will enter data into the mobile application.

Measuring Length (National operational guidelines for CMAM Nigeria)

How to measure LENGTH (when lying down) If the child is less than 87cm, he/she should be measured lying down.

1. One person holds the child's head, making sure the child's head is touching the back of the board. The child's eyes should be looking straight up.
2. The other person holds down the child's knees, pressing the sliding wood piece against the child's heels and soles of the feet.
3. Align the child with the board
4. Child's arms should be lying alongside his/her body, and if necessary, the mother can hold the arms down
5. The person holding the feet reads the measurement.

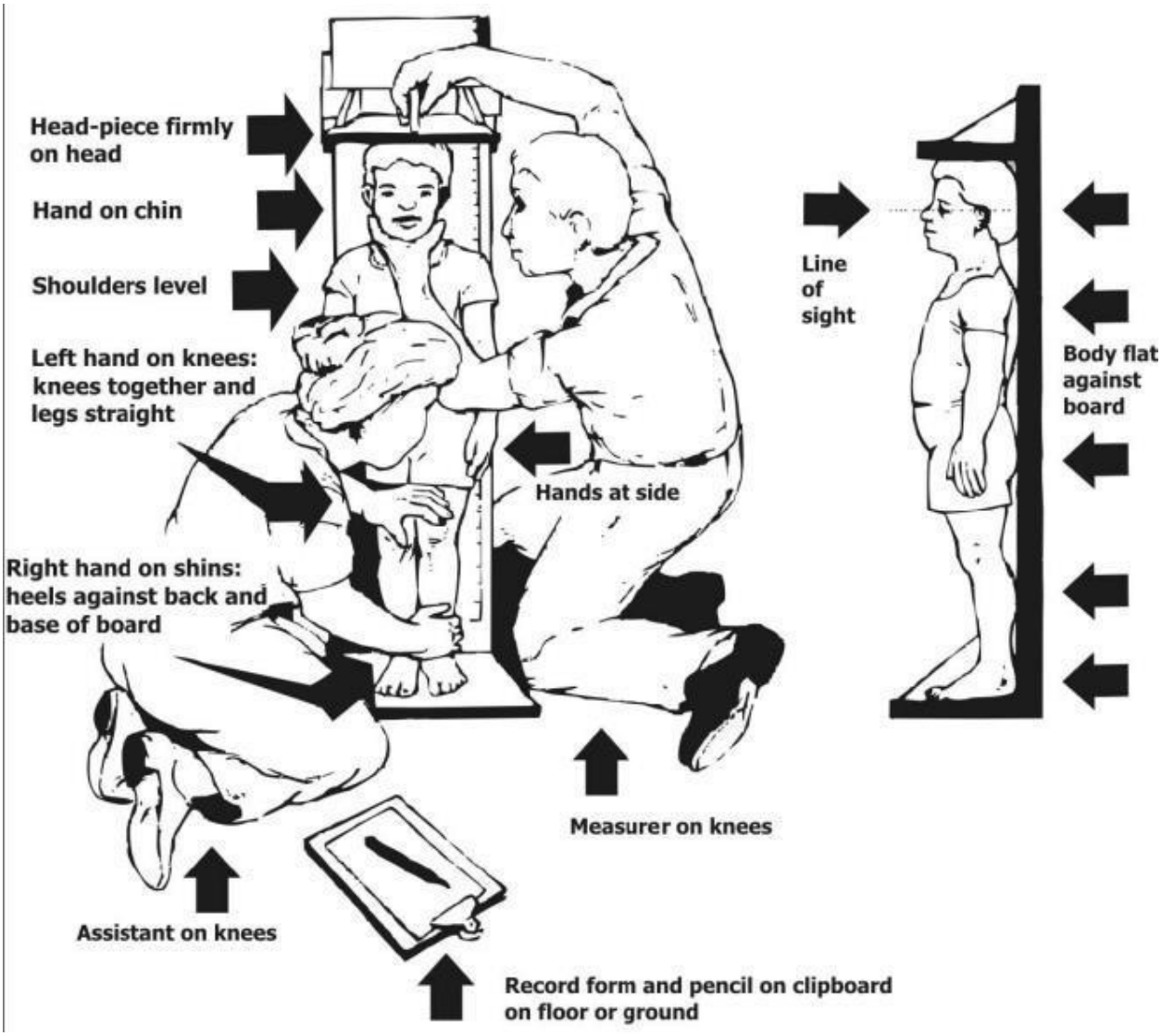


Measuring Height (National operational guidelines for CMAM Nigeria)

How to measure HEIGHT (when standing) If the child is more than 87cm, he/she should be measured standing.

1. Place the child's feet flat and together in the centre of and against the back and base of the wall.

2. One person places their right hand just above the child's ankles on the shins, left hand on the child's knees and push against the wall. Make sure the child's legs are straight and the heels and calves are against the wall
3. Tell the child to look straight ahead making sure the child's line of sight is level with the ground.
4. The second person should place their open left hand under the child's chin. Do not cover the child's mouth or ears. Make sure the shoulders are level, the hands are at the child's side, and the head, shoulder blades, and buttocks are against the wall.
5. When the child's position is correct, person holding the legs reads (at eye level) and call out the measurement to the nearest 0.1 cm.



Measuring Weight

Tempered glass digital standing scales will be used to weigh infants and children to the nearest 0.1 kg.

For infants and children who cannot stand:

1. Before weighing the child, take all his/ her clothes off
2. Zero the scale
3. Ask the mother to step onto the scale and record her weight in the mobile app.
4. Place the child into her arms.
5. Record the total weight in kg to the nearest 0.1 kg and enter into the mobile app. The app will calculate the weight of the child.
6. Do not hold the scale when reading the weight

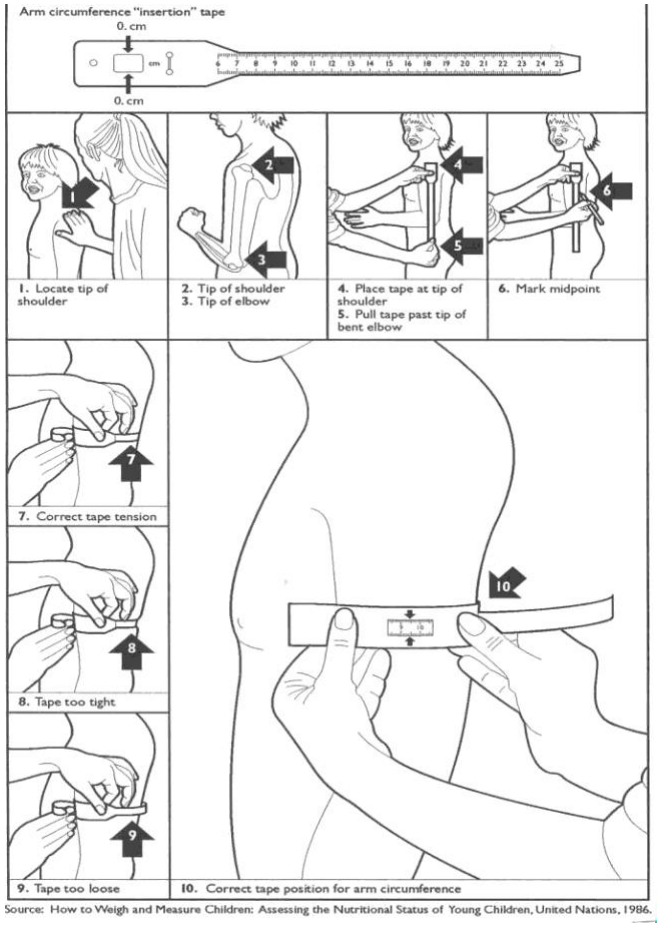
For children who can stand:

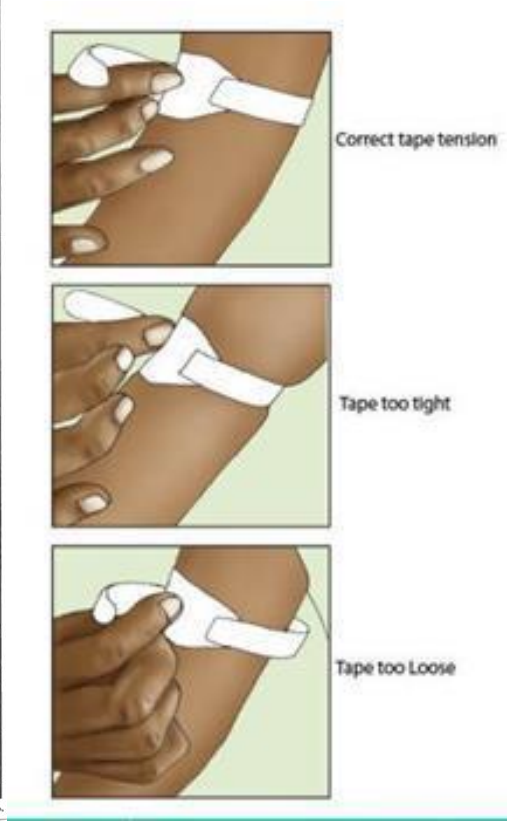
7. Before weighing the child, take all his/ her clothes off
8. Zero the scale
9. Ask the child to stand on the scale
10. Make sure the child is not holding onto anything
11. Record the weight in kg to the nearest 0.1 kg in the mobile app
12. Do not hold the scale when reading the weight

Measuring Mid-Upper Arm Circumference (National operational guidelines for CMAM Nigeria)

The child's MUAC will be measured **three times**. MUAC measurements will be taken at the midpoint of the **left** arm between the tip of the shoulder and the tip of the elbow using non-stretch MUAC tapes.

1- Find the midpoint. Ask the patient to stand, or for a small child, have the caregiver hold the child, with the patient's left arm bent at a 90-degree angle. Find the bone that forms the tip of the shoulder (acromion process), and place the zero point of the MUAC measure there (it is usually the middle of the window). Extend the MUAC tape down to the tip of the elbow (olecranon process). Read the length in mm of this distance between shoulder and elbow; then divide this number in half to find the mid-point (or fold the tape in half between the zero and the elbow point). Mark the mid-point in pen on the patient's arm.
2- Position the patient to read the MUAC. Have the patient stand or sit with the left arm hanging loosely by the side of the body. Muscles should not be flexed at all.
3- Measure the MUAC. Place the MUAC tape around the left arm at the midpoint mark. It should fit snugly around without constricting the arm. Read the measurement from the window of the tape. Take the measurement to the nearest 0.1cm.





3.4 Malaria Rapid Diagnostic Test

Malaria infection status will be assessed on all enrolled children using a rapid diagnostic test (RDT) at baseline.

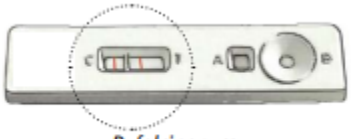
Supplies

- Mobile data collection device & accessories
- RDT test packet
- Alcohol swabs
- Gloves
- Lancet
- Buffer
- Timer

Conduct the Malaria RDT

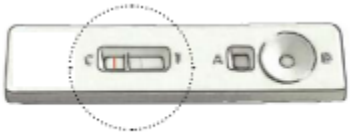
1. Check the expiry date on the test packet. If the expiry date has passed, choose another packet that has not yet expired.
2. Put on the gloves. Use new gloves for each patient.
3. Open the packet and remove:
    a. The test
    b. The capillary tube
    c. The desiccant sachet

4. Write the patient's name and study ID number on the test
5. Open the alcohol swab. Grasp the 4th finger on the patient's left hand. Clean the finger with the alcohol swab. Allow the finger to dry before pricking.
6. Open the lancet. Prick patient's finger to get a drop of blood.
7. Discard the lancet into an appropriate sharps receptacle immediately after pricking the finger.
8. Use the capillary tube to collect the drop of blood.
9. Use the capillary tube to put the drop of blood into the square hole on the test marked "A."
10. Discard the capillary tube into an appropriate sharps receptacle
11. Add 6 drops of buffer into the round hole marked "B."
12. Wait 15 minutes after adding buffer
13. Read test results. Do NOT read the test sooner than 15 minutes after adding the buffer. You may get false results
14. How to read the test results:
    a. POSITIVE: a line near letter "C" and a line near letter "T" means the patient is positive for malaria.



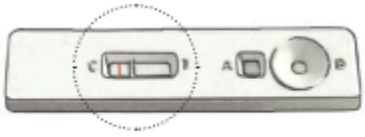
P. falciparum

    i. The test is positive even if the line near "T" is faint



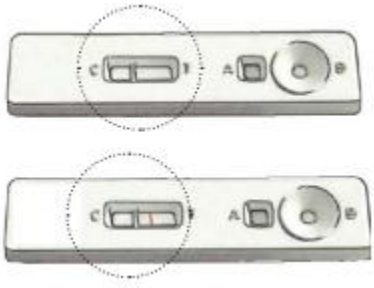
P. falciparum (faint +)

    b. NEGATIVE: a line near letter "C" and NO LINE near letter "T" means the patient does NOT have malaria



Negative

    c. INVALID RESULT: NO LINE near letter "C" and one or no line near letter "T" means the test is INVALID



    i. Repeat the test using a new RDT and a new lancet if no control line appears
15. Dispose of gloves, alcohol swab, desiccant sachet, and packaging

16. Record the test result in the mobile application.

3.5 Assess for bilateral pitting oedema

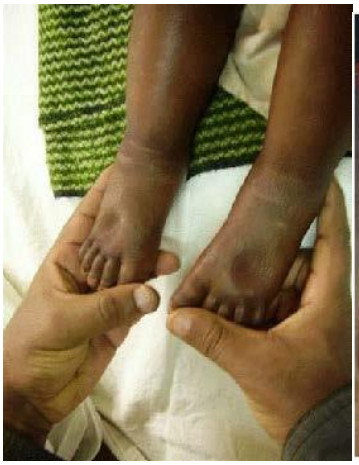
Assessing for oedema will be done at enrollment to ensure eligibility and will also be assess at each weekly visits

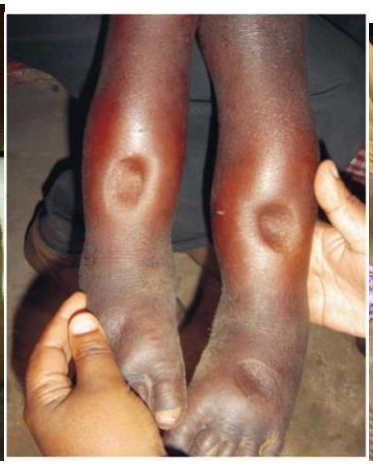
1. While child is sitting, grasp both feet in your hands. Apply firm thumb pressure to the tops of both feet for three full seconds (count 101, 102, 103). Remove the thumbs.
2. If the depression from your thumbs remains on both feet, then the patient has bilateral pitting oedema. It may be easier to feel this depression than to see it.
3. If tops of feet are edematous, repeat the process on the shins and hands.
4. If the shins / hands are edematous, observe for oedema around the eyes.

Oedema is nutritionally significant if it is present on both feet. However, bilateral pitting also be caused by medical conditions such as nephritic syndrome. Medical causes should be first ruled out before the diagnosis of nutritional Oedema is made.

Grades of oedema

Grade of oedema	Observation
Absent	Absent, no oedema
Grade +	Mild: both feet / ankles
Grade ++	Moderate: both feet + lower legs
Grade +++	Severe: generalized oedema including both feet, legs, hands, arms and face/head


Grade +


Grade ++


Grade +++

Only children with grade + and grade ++ will be eligible to participate in the study.

3.6 Vital Status

Vital status will be recorded at all follow-up visits up to 12 weeks after inclusion. Information about whether the child is alive, has died, or has moved will be recorded. Date of death and location of move will be recorded.

3.7 Clinical examination

Outcomes of clinical examinations will be collected at enrollment, weekly follow-up visits, and at week 8. Clinical examinations will be conducted according to the standard of care in the management of SAM. Recorded outcomes include diagnoses made and treatments given/recommended.

4. STUDY MEDICATION

Children enrolled in the study will be offered weight-based, directly observed, oral suspension azithromycin plus placebo or a short course of oral amoxicillin. We will monitor adverse events following treatment as described in Section 5.

4.1 Study Medication Description

The azithromycin used in the trial will be suspension Azithromycin (Everdestiny) made by Everdestiny Pharmaceutical Limited.

The oral amoxicillin routinely used at each OTP for treatment of uncomplicated severe acute malnutrition, which is suspension Amoxicillin (Emzor) by Emzor pharmaceuticals limited, will be used for this trial.

The placebo used in this trial to mask participants in the azithromycin arm will be made by a local pharmacy.

All medications and placebo used in the trial will be placed in generic bottles at the local pharmacy to blind participants to the trial arm. The study nurse and investigators will be unblinded to the bottles

4.2 Dosage Information

Azithromycin will be administered as a single dose, in oral suspension form for children. Dosing will follow the WHO recommendations for treatment of active trachoma: Single dose of 20mg/kg in children (up to the maximum adult dose of 1g).

The placebo given to individuals in the azithromycin arm will be instructed to administer the placebo at a volume equivalent to the amoxicillin dose.

Individuals who are allergic to macrolides/azalides will not be treated.

Oral amoxicillin will be administered for 5 days. The first dose will be administered by the health agent, who will teach the caregiver how to administer the medication at home. The remaining doses will be administered by the caregiver.

Amoxicillin will be administered at a dose of 40mg/kg twice per day for 5 days.

4.3 Medication Procurement

Azithromycin, placebo, and amoxicillin will be purchased locally in Nigeria by the study team. Enrolled participants will incur no costs associated with the study medication.

4.4 Medication Quality Control

Study medication will be stored at each site prior to use. The study team and site staff will regularly check and record the study medication expiration dates. The expiration dates on the medication containers will be strictly monitored and all expired study medicine will be discarded appropriately. The study coordinator will work with each health facility to ensure that they have appropriate stock of all study medications.

5. ADVERSE EVENTS

5.1 Adverse Event Monitoring and Reporting

Parents or guardians of enrolled children will be instructed to report any adverse events experienced within the 7 days following the enrollment visit, by phone or in person. At all follow-up visits, study staff will inquire about the child's experience of adverse events, including if the child had any of the following symptoms:

- Fever
- Diarrhea
- Vomiting
- Abdominal pain
- Skin rash
- Constipation

The study team will assess whether the parent or guardian sought care for the child since the last visit and if so, what the reason was for the health care visit and if the child was hospitalized.

Serious adverse events will be defined as death, hospitalization, or any other life-threatening situation. Serious adverse events will be reported to the Medical Monitor within 24 hours.

The health agent conducting the follow-up visit will email the Taimaka investigators if a serious adverse event is diagnosed, the Taimaka investigators will immediately email the Medical Monitor and the UCSF study team. The Medical Monitor will make a determination as to whether the event could be reasonably considered to be related to the study drug and will report the results of this determination to the study investigators, who will report to the UCSF IRB and the DSMC as needed. Information on all adverse events, serious and non-serious, will be recorded on data collection forms through the mobile application.

See Appendix 5 for more information on SAE reporting.

5.2 Inpatient Hospitalization Transfer Information

OTP staff will screen children for conditions requiring referral to hospital care. Referrals will occur at multiple points, including:

1. Enrollment
2. All follow up visits

Pathways to the ITP (Inpatient Treatment Program):
SAM patients are referred to the ITP using a referral card, and their expenses are paid by the Taimaka Project.

Referrals during Triage
Triage refers to the process of identifying patients in need of urgent treatment. Triage will occur in the OTP waiting area and should be conducted as soon as possible after caregivers and children arrive. During triage, OTP staff complete two main steps:

1. Identify children with danger signs and immediately refer them to hospital care.
2. Check children for signs of measles and immediately isolate suspected cases.

Emergency Health Check:
On arrival at the OTP waiting area, each child will be immediately assessed for danger signs, which are health conditions that require urgent hospital care. Danger signs include:

1. Unconscious
2. Lethargy, not alert
3. Unable to move/extreme weakness
4. Convulsions/fits/seizures
5. Difficulty breathing

For children enrolled in the trial who exhibit any of these signs, a triage assistant will assign the child a registration number and fill out the referral form and admissions form with basic information such as the name of child and caregiver, admissions number, and phone number, and accompany the child and caretaker to the ITP.

Referrals during Anthropometric Assessment
In some cases, conditions identified during anthropometric assessment should prompt a referral to the ITP. These fall into three main categories:

1. Any child with grade 3 (+++) oedema should receive a urinalysis test strip to measure protein. If the result is less than 2, they should be referred to the ITP.
2. Any child <6 months who has SAM should be referred to the ITP.
3. At weekly visits, children showing certain signs of non-response should be referred to the ITP.

Oedema:
Any child with grade 3 (+++) oedema should be referred to the ITP. Additionally, OTP staff should request a urinalysis test for children with grade 1 (+) or grade 2 (++) oedema. This test will be carried out by the lab assistant. The results of this test will be used to identify non-nutritional causes of oedema, such as kidney problems. A protein result of >2 indicates that the child may have non-nutrition oedema. Children with non-nutritional oedema should be advised to visit a hospital to check for other health problems. These steps are outlined in the table below.

Additionally, because nutritional oedema begins in the feet and moves upward, caregivers should also be asked where the oedema began. If it did not begin in the feet, advise the caregiver to visit a hospital.

SAM patients should be referred to the ITP in the event of:

Criterion	**Time after admission into OTP**
Severe complications (defined in next lecture)	At any visit
Failure to gain any weight (non-edematous children)	21 days
Weight loss since admission to program (non-edematous children)	14 days
Failure to start to lose edema	14 days

Edema still present	21 days
Weight loss of 5% of body weight (non-edematous children)	At any visit
Failure of appetite test	At any visit
Failure to start to gain weight satisfactorily after loss of edema (kwashiorkor) or from day 14 (marasmus) onwards. Satisfactory is determined as ‘at least 5 g/kg of body weight per day.’	At any visit
Failure to gain weight (rule out RUTF sharing, selling, other noncompliance, etc.) (non-oedematous children)	Any 14 day interval
Weight loss for two successive visits	At any visit
No MUAC gain for two consecutive weeks	At any visit

6. DATA COLLECTION, MANAGEMENT, AND SECURITY

6.1 Data Collection

Data will be collected on enrolled children at baseline (time of enrollment), and follow-up weeks 1-12. Written informed consent will be collected on paper and the study officer administering treatment will record treatment administration on Taimaka's internal ap. All other data will also be collected electronically on mobile devices using ODK mobile application.

Data from the study participants is stored in the same database as data from all of Taimaka's patients. Taimaka will share the entire database with UCSF, and the UCSF study team will write a carefully-worded statistical programming script to only select records and data of the study participants.

6.2 Data Management and Security

Electronic data will be uploaded daily to a secure, password-protected, cloud-based server hosted by Taimaka. All devices used for data collection will be password-protected, as will the mobile application itself. Paper forms will be stored in locked cabinets accessible only by specific study team members at each enrollment site.

Study indicators and PII will be collected electronically and stored securely in Taimaka's password-protected, cloud-based server. Study data will only be accessible by study team members and investigators in order to protect confidentiality.

6.3 Data Quality and Monitoring

All study team members collecting data will undergo an initial training to learn how to use the mobile devices as well as best practices for data collection. Data collection will be monitored on a weekly basis by the study team. Concerns over data quality and completeness will be relayed to the local study team by email, and refresher trainings and/or additional supervision of data collection by local investigators will be planned as needed. The study team will send quarterly progress reports to the DSMC, including aggregate data on enrollment and follow-up status, weight gain, nutritional recovery, and adverse events.

7. PROTECTION OF HUMAN SUBJECTS

Before any study procedures are implemented, the study team will obtain Institutional Review Board (IRB) approval from committees at UCSF and Nigeria. In addition, local study team members will approach each potential enrollment site to describe the study and obtain their consent to participate as a study site. At the individual level, study personnel will obtain written informed consent from at least one parent or guardian for all study activities. Any guardians who are illiterate will be provided an impartial witness to explain the consent form at the time of enrollment. If, at any time, a parent or guardian elects to withdraw a child from the study, they will be free to do so. Individuals who withdraw will be offered the same standard of care outside the study.

7.1 Institutional Review Board Approval

University of California, San Francisco (UCSF) Committee on Human Research
UCSF's Committee on Human Research will annually review the study protocol for ethical approval.

Gombe State Ministry of Health
The study protocol will be reviewed and granted ethical approval by these 2 committees in Nigeria before any study activities begin.

7.2 Informed Consent

Study personnel fluent in relevant local languages will approach parents or guardians of eligible children at the enrollment site. In a private setting, the study team member will explain the objectives, risks, and benefits of the study as well as detailed information about what study participation entails for the child and the parent or guardian. The study team member will clarify that participation in the study is voluntary, that participation may be stopped at any time, and that all collected data will be kept confidential and securely stored. The study team member will ensure comprehension by inviting the parent or guardian to ask questions and will provide time for the parent or guardian to consider participation. Any guardians who are illiterate will be provided with an impartial witness to explain the consent form. When providing consent, both the study team member and the parent or guardian will sign two copies the consent document. One copy will be given to the parent or guardian and the other will be kept for study reference.

8. DATA AND SAFETY MONITORING COMMITTEE

The Data and Safety Monitoring Committee (DSMC) will consist of independent experts in biostatistics, epidemiology, child health and nutrition, and/or global public health.

The DSMC will be empaneled prior to the beginning of the study. The committee will meet once prior to the start of the study and at the study's conclusion. All study protocols will be subject to review and approval by Institutional Review Boards at UCSF and Nigeria, and by the DSMC.

The DSMC will be notified in real time of serious adverse events (SAEs). They will notify the study team if they would like to receive information about SAEs in a different manner. Committee members will monitor any sever or unexpected trend that threatens the safety of study participants. The DSMC will be authorized to end the study if they deem necessary (e.g., safety, feasibility).

The study team will send the following reports to the DSMC:

- A report at 1 month post-enrollment
- A report when 50% of the enrollment target has been reached (at 300 participants enrolled)
- A study close-out report at the end of the study

A study closeout meeting will be scheduled at the end of the study unless deemed unnecessary.

9. STATISTICAL METHODS

9.1 Sample Size and Power

Specific Aim 1 We assume that inclusion of 600 children (300 randomized to each arm) will provide 80% power to detect a 15% increase in weight gain (g/kg/day) in children receiving azithromycin compared to children receiving amoxicillin at an alpha of 0.05. Assumptions for this calculation were based on the pattern of weight gain reported in a trial of routine amoxicillin for uncomplicated SAM in Burkina Faso comparing children receiving azithromycin to amoxicillin over time.[11] We assumed an average weight gain of 2.6 g/kg/day over 8 weeks in the amoxicillin arm, with a standard deviation of 1.7 g/kg/day, and loss to follow-up of 10%. A 16% increase corresponds to a mean difference in weight gain of 0.4 g/kg/day, or an average weight gain of 3.0 g/kg/day in the azithromycin arm.

This calculation was performed in Stata using the following command:

power twomeans 2.6, sd(1.7) alpha(0.05) power(0.8) n(540)

Specific Aim 2. Inclusion of 600 children (300 randomized to each arm) will provide 80% power to detect a 12 percentage point difference in the proportion of children achieving nutritional recovery in the azithromycin arm compared to the amoxicillin arm. Assumptions for this calculation were based on nutritional recovery reported in the amoxicillin arm of a trial of routine amoxicillin compared to azithromycin for uncomplicated SAM in Burkina Faso.[11] We assumed that 36% of children in the oral amoxicillin arm would achieve nutritional recovery and a loss to follow-up of 10%.

This calculation was performed in Stata using the following command:

power twoproportions 0.36, alpha(0.05) power(0.8) n(540)

9.2 Statistical Analysis

Baseline characteristics. Characteristics of the study population collected at baseline will be summarized using frequencies and percentages for categorical variables and means and standard deviations or medians and inter-quartile ranges for continuous variables. Baseline characteristics will be compared by treatment arm using Fisher's exact test for categorical variables and t-tests or Wilcoxon rank-sum tests for continuous variables.

Specific Aim 1. The primary analysis will compare weight gain velocity (g/kg/day) between groups over the 8-week follow-up period. We will estimate mean differences and 95% confidence intervals for the difference using a linear regression model with an indicator for study group.

$$E[Y \mid X = x] = \beta_0 + \beta_1 X + e$$

Where:

- Y **= weight gain velocity from enrollment to 8 weeks**
- X = binary indicator for treatment group (X=1 for azithromycin, X=0 for a short course of oral amoxicillin)

- β_1 **= difference in weight gain velocity between the azithromycin group compared to a short course of oral amoxicillin group**
- $e \sim N\ (0, \sigma^2)$

Sensitivity analyses will include similar linear models to assess period-specific weight gain by group from week 0-1, 1-2, 2-4, and 4-8.

Specific Aim 2. The primary analysis will compare nutritional recovery by 8 weeks from baseline by arm. We will use log-binomial regression for this analysis to estimate the risk ratio. We will use the following model:

$$log[P(Y = 1|X_1 = x_1] = \beta_0 + \beta_1 X_1 + e$$

Where:

- Y **= binary indicator for nutritional recovery by 8 weeks (Y=1 for recovered, Y=0 for not recovered)**
- X = binary indicator for treatment arm (X=1 for azithromycin, X=0 for a short course of oral amoxicillin)
- e^{β_1} **= relative risk of nutritional recovery in azithromycin arm compared to a short course of oral amoxicillin arm**
- $e \sim N\ (0, \sigma^2)$

If the log-binomial model fails to converge, we will use a modified Poisson model with robust standard errors as an alternative.

Secondary outcomes.

Time to event outcomes (time to recovery and time to mortality) will be assessed visually using Kaplan-Meier curves and compared by arm using the log-rank test.

Binary outcomes will be analyzed using modified Poisson regression for rare outcomes (e.g. mortality) or log-binomial regression for common outcomes (e.g. malaria), using models similar to the one described above for Specific Aim 2.

Anthropometric assessments will be analyzed using linear models as described for Specific Aim 1, with correction for baseline values. For anthropometric assessments, z-scores will be calculated based on the 2006 WHO Child Growth Standards. Anthropometric z-scores will be analyzed as continuous variables and secondary analyses will explore categorization.

All analyses will be intention-to-treat. A significance level of 0.05 for inference and 95% confidence intervals will be reported for all effect estimates. All analyses will be conducted using R (R Foundation for Statistical Computing, Vienna, Austria). For all models, model diagnostics will be conducted to assess appropriate fit.

Missing data.

If ≤10% of enrolled children is missing outcome data, complete case analyses will be conducted. If >10% of enrolled children are missing outcome data, inverse probability weighting will be used to weight complete cases by the inverse of an estimate of the probability of an outcome being observed as a sensitivity analysis. Weights will be constructed with the following

baseline characteristics chosen as factors likely to predict follow-up: SES, distance from health center, WHZ, and MUAC.

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PROTOCOL UPDATES

Date	Changes
Oct 7 2022	● Clarified inclusion and exclusion criteria (Section 2.2 & 2.6) ● Clarified weight measurement (Section 3.2) ● Clarified that illiterate guardians require impartial witness to explain consent (Section 7 & 7.2) ● Added more information on DSMC roles and responsibilities (Section 8) ● Clarified SAE report flow (Appendix 5) ● Added referral criteria for transfer to inpatient care for SAM participants (Section 5)
Nov 28 2022	● Added Taimaka database access (Section 6.1 and 7.2) ● Fixed grammatical errors throughout
February 9 2023	● Updated Taimaka database access language per discussions with IRB (Section 6.1 and 7.2)
April 19, 2023	● Updated eligible recruitment sites information (Section 2.2)

APPENDIX