Azithromycin as Adjunctive Therapy for Uncomplicated Severe Acute Malnutrition: An individual-randomized pilot trial of the effect of a single dose of oral azithromycin on weight gain in children with uncomplicated severe acute malnutrition in Burkina Faso

Manual of Operations and Procedures

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ABBREVIATIONS

CHW: Community Health Worker
CSPS: Centre de Santé et de Promotion Sociale
DSMC: Data and Safety Monitoring Committee
HAZ: height-for-age z-score
IRB: Institutional Review Board
MUAC: mid-upper arm circumference
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 Burkina Faso 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 with receive non-antibiotic routine care for uncomplicated SAM in Burkina Faso, which includes 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 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

The proposed study is a pilot trial conducted in preparation for a future, larger trial. 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 nutritional programs at health centers in Burkina Faso 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 Burkina Faso, which includes therapeutic feeding with ready-to-use therapeutic food (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.

2.1. Study Setting

The trial will be conducted at Centre de Santé et de Promotion Sociale (CSPS) that run nutritional programs for children presenting with SAM. CSPSs are government-run integrated health centers linked to and overseen by district hospitals.

2.2. Recruitment and Eligibility Criteria

Recruitment

Community health workers (CHWs) will be trained by the study team to actively seek cases of SAM in the study area and refer them to a study CSPS. CHWs will screen for SAM using tape to measure mid-upper arm circumference (MUAC) and will refer children with MUAC < 115 mm to a study CSPS.

Each participating enrollment site will be assigned at least one dedicated study team member who will enter data and conduct outcome assessments. The study team member will be either an existing member of enrollment site staff who will be trained for the study or an external study team member who will be placed at the site for the duration of the study.

This study team member will review the site logbook and/or medical records every day to identify children who are potentially eligible for participation, including both children referred by CHWs and children presenting independently. The team member will approach the parent or guardian of potentially eligible children to confirm eligibility according to the criteria listed below.

Eligibility criteria for enrollment sites

For inclusion in the pilot trial, sites must meet the following criteria:

1. More than 200 cases of severe acute malnutrition seen in 2017
2. Willing to participate in the trial
3. Participation approved by the district

Eligibility criteria for individuals

Eligible individuals are children aged 6-59 months with SAM who present to an eligible enrollment site 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
- No nutritional edema
- Primary residence within catchment area of enrollment site
- Available for full 8-week study
- Has not been admitted to a nutritional program for the treatment of SAM in the 2 preceding weeks
- No antibiotic use in past 7 days
- No clinical complications requiring antibiotic treatment
- No clinical complications requiring inpatient treatment
- No 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, etc)
- No allergy to macrolides/azalides
- 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
- 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, 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 local trained study personnel. At enrollment, children will be assigned a study identification number using the next unassigned number on a list identification numbers assigned to the site. Enrolled children will then undergo a baseline assessment. The baseline assessment includes data collection on demographics and socioeconomic status, anthropometric assessments, and a malaria rapid diagnostic test (RDT; see Figure 1 and Section 3 for details). After completion of the baseline assessment,

children will be randomized to receive either a single dose of directly observed oral azithromycin or a 7-day course of oral amoxicllin.

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 or a short course of oral amoxicillin. The randomization sequence will be linked to the study identification numbers. Randomized study arm assignments will be placed in sealed, opaque envelopes labeled with study identification numbers. When a child has been enrolled and has completed the baseline assessments, a CSPS nurse trained for the study will open the envelope to determine the allocation, and will administer study medication indicated as described in Sections 2.4 and 4.

To keep the allocation concealed, only the study nurse administering treatment will have access to the envelopes with the randomization allocations. The study nurse will open the envelope and administer treatment in a private room without the outcome assessor present. For each enrolled child, the study nurse will record whether or not azithromycin was administered on a paper form kept in a locked cabinet not accessible by the outcome assessor.

Given the nature of the intervention, participants and study personnel administering treatment will not be masked to treatment assignment. Outcome assessors will be masked to treatment assignment; this will be accomplished by assigning one CSPS nurse to administer treatment and a separate masked study team member to perform outcome assessments, including anthropometry, malaria RDT, and vital status updates.

2.4. Interventions

Children will be randomized to receive a single, directly observed dose of oral azithromycin or a short course of oral amoxicillin, which 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 Burkina Faso, which includes RUTF (170 kcal per kilogram per day; Plumpy'Nut, Nutriset). In Burkina Faso, standard treatment includes weekly follow-up visits to monitor anthropometric indicators. Enrolled children will be followed weekly at each routine clinic follow-up visit until nutritional recovery and again at 8 weeks following admission.

Standard of care of the outpatient management of SAM in Burkina Faso includes a short course of oral amoxicillin. Children enrolled in this study will not receive oral amoxicillin, regardless of randomization assignment.

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).

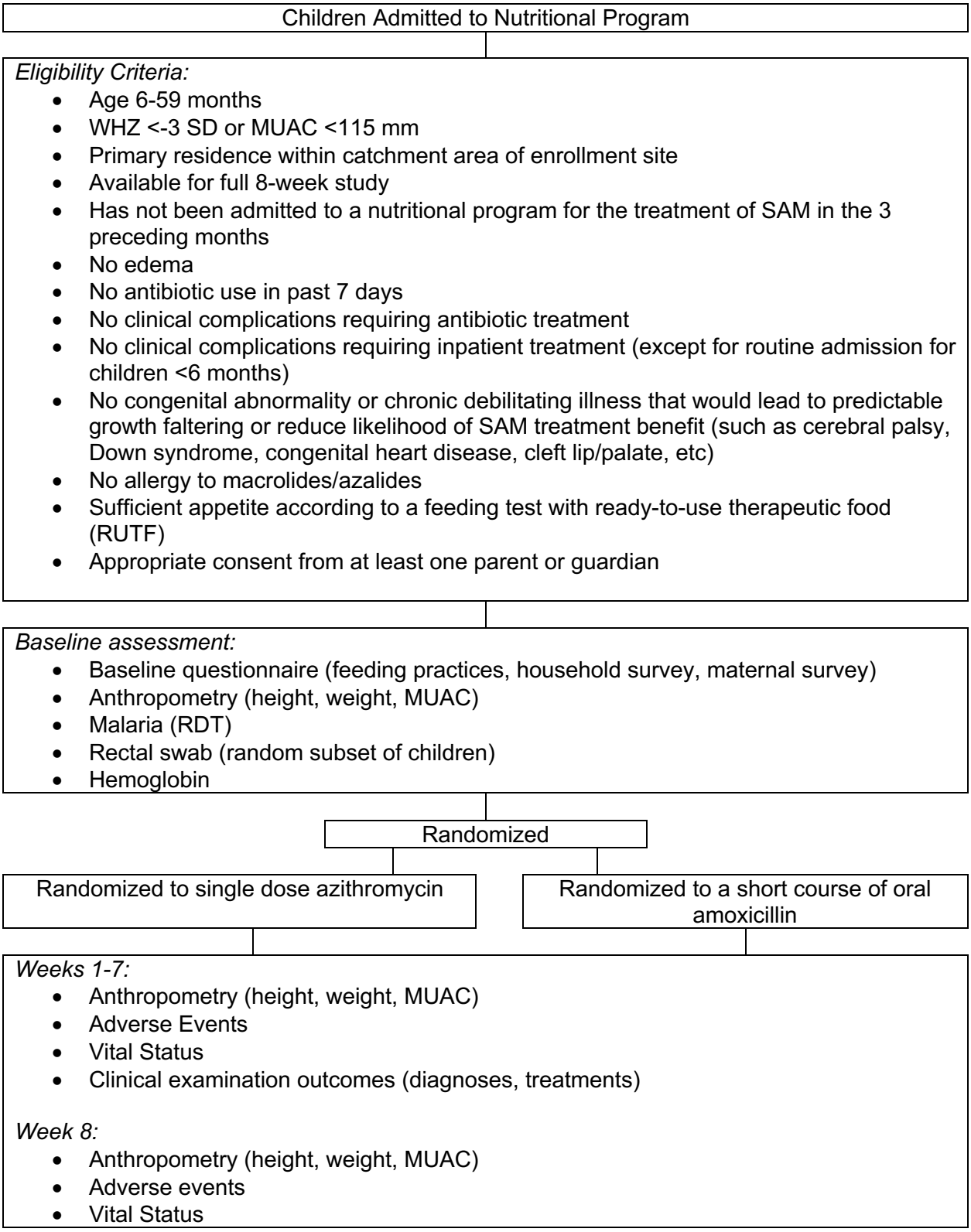
Secondary Outcomes

- **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 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.

- **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.
- **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 (defined in Section 5).
- **HAZ.** Height or length will be measured at all follow-up time points 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.
- **Intestinal microbiome:** Rectal swabs will be collected in a random subset of children at baseline and at week 8.

2.6. Participant Timeline

Figure 1. Participant Timeline and Flow



• Malaria (RDT) • Rectal swab (random subset of children) • Hemoglobin • Clinical examination outcomes (diagnoses, treatments)

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 UCSF investigators. The UCSF investigators will design and implement trainings for study procedures and maintain weekly communication with local Burkina Faso study staff.
- **Investigators (CRSN).** The CRSN 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 Burkina Faso 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. The Medical Monitor will participate on the Data and Safety Monitoring Committee.
- **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 (CRSN).** Study Team Members at CRSN will be responsible for implementation of all study procedures as described in Section 3, including recruitment, consent, enrollment and randomization, drug administration, and collection of all study data, including anthropometric and malaria assessments.
    - **CSPS Nurse.** A nurse at each CSPS will be trained to determine the randomization allocation of enrolled children by opening the envelopes and to administer azithromycin if indicated.
    - **Outcome Assessor.** One outcome assessor for each site will be trained to manage consent, enrollment, and collection of all study data, including outcome assessments.

3. PROCEDURES

3.1. Training

All study personnel participating in study procedures (including enrollment and baseline assessment, randomization, drug administration, outcome assessments, and data collection) will participate in a 2-day initial training. Training will include a mix of lecture and practice. Participants must achieve a score of >80% on the training quiz in order to participate in the study and demonstrate agreement with a gold standard grader for all anthropometric assessments. Study personnel will be overseen by study investigators during the first week of enrollment, and refresher training will be conducted once a month during the course of the study.

3.2. Anthropometry

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

Supplies

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

Anthropometry Team

Two study team members 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 and Height

A lightweight measuring board will be used to measure the participant's height to the nearest 0.1 cm. Height and length will be assessed with a ShorrBoard. Depending on a child's age and ability to stand, measure the child's length or height.

- **Length:** If a child is less than 2 years old, or cannot stand alone, measure recumbent length. The recorder will select **Length** in the application to indicate that length was measured. A child's length is measured lying down (recumbent).
- **Height:** If a child is able to stand, measure standing height. The recorder will select **Height** in the application to indicate that height was measured. Height is measured standing upright.

If the child has braids or hair ornaments that will interfere with length/height measurements, remove them if possible. Check that any sandals, shoes, or socks have also been removed. Whether measuring length or height, the mother/guardian is needed to help with measurements and to soothe and comfort the child. Explain to the mother the reasons for the measurements, and describe the steps in the procedure. Answer any questions she might have. Show her and

tell her how she can help you. Explain that it is important to keep the child still and calm to obtain the best measurement.

ShorrBoard Set-Up

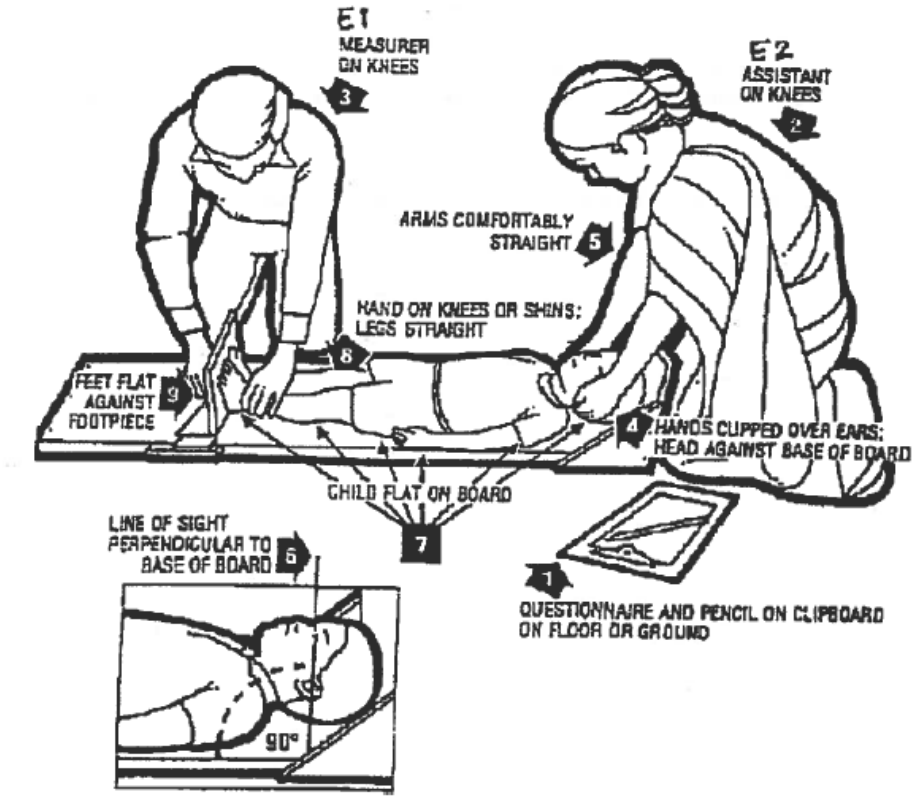
1) Remove ShorrBoard from bag.
2) Stand the ShorrBoard upright. You can step on the base of the board to keep it stable.
3) As you face the board, turn the non-removable bolt counterclockwise to release the extension piece. Note: the bolt remains attached to the back of the extension piece – do NOT remove it.
4) Slide the extension piece into the top end of the main board and fasten the clasp on the back of the board. Make sure the clasp is fastened properly.
5) The auto-lock sliding head/footpiece is stored in the base of the main board and can be moved up and down the length of the measuring board. It should stay in place on its own wherever you position it.
6) The measuring board must be placed against a firm surface for standing height (e.g. wall, table, tree, against a vehicle, etc.). Make sure the board is stable. If necessary, place items such as small rocks underneath the height board to stabilize it during the measurement.
7) Clean the equipment with alcohol swabs at the beginning of each day, and clean with alcohol swabs between each participant.

Note: when you set up the board each day, examine each of the pieces to check for damage.

Measure Length

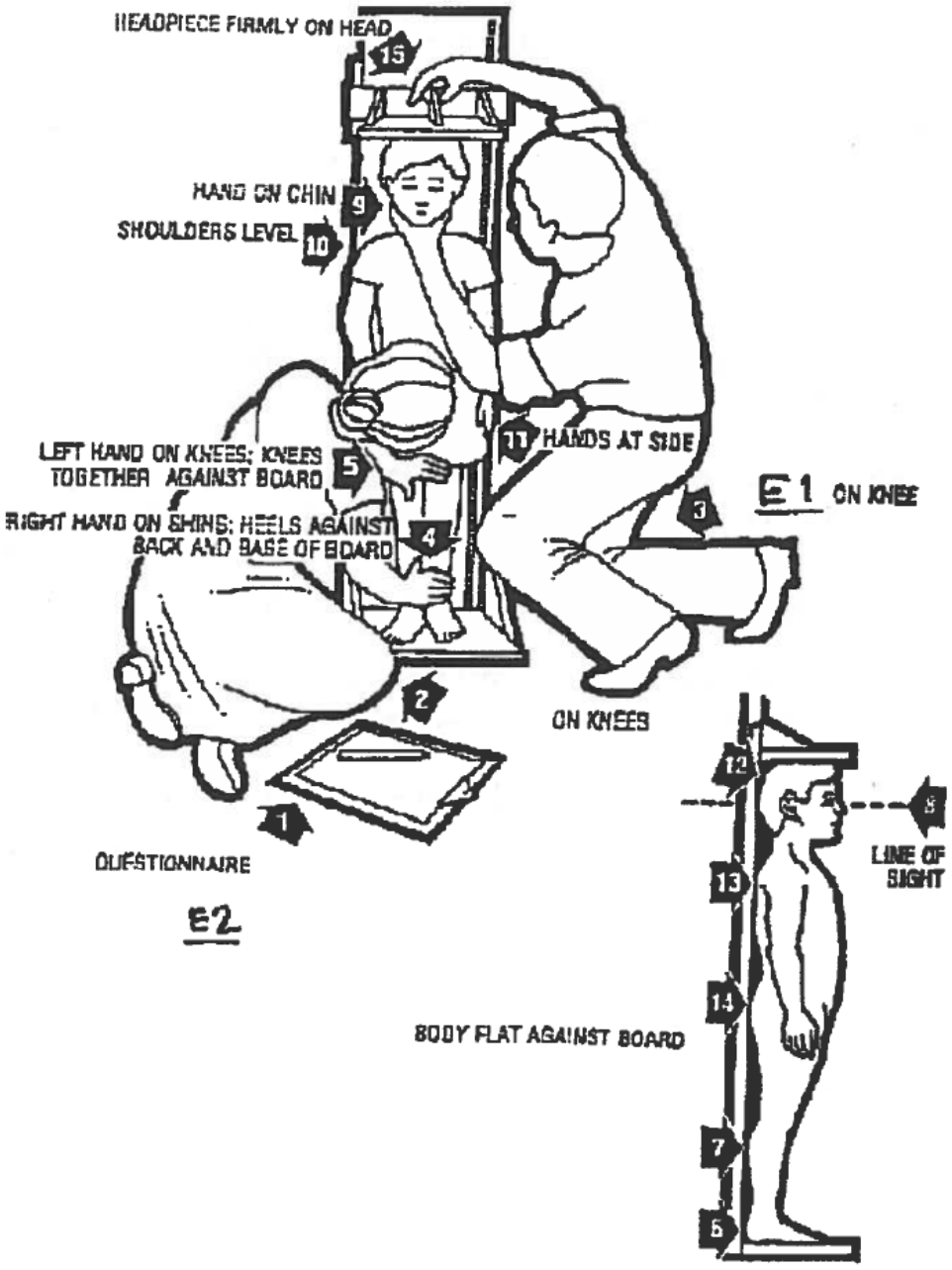
1. Cover the length board with a chuck for hygiene and for the baby's comfort.
2. We usually have the assistant anthropometrist hold the baby's head and the lead anthropometrist manage the legs and feet. The mother stands to the side and focuses primarily on soothing the baby. The lead anthropometrist calls out the measurement and the assistant repeats it and then records it on the tablet.
3. Ask the mother to stand nearby and focus on soothing the baby.
4. The assistant anthropometrist will place the baby on the length board on his/her back with his/her head fixed against the headboard, compressing the hair and will hold the baby's head in place while the measurement is taken. The assistant should move quickly and surely without distressing the baby.
5. The assistant anthropometrist will quickly position the head so that an imaginary vertical line from the ear canal to the lower border of the eye socket is perpendicular to the board. (The child's eyes should be looking straight up.)
6. **Speed is important.** The lead anthropometrist will manage the baby's legs and feet. Standing on the side of the length board where you can see the measuring tape and move the footboard:
    a. Check that the child lies straight along the board and does not change position.
    b. Shoulders should touch the board, and the spine should not be arched. Ask the mother to inform you if the child arches the back or moves out of position.
    c. Hold down the child's legs with the one hand and move the footboard with the other. Apply gentle pressure to the knees to straighten the legs as far as they can go without causing injury or distress. **Note: it is not possible to straighten the knees of newborns to the same degree as older children. Their knees are fragile and could be easily injured, so apply only gentle pressure.**

   d. If a child is extremely agitated and both legs cannot be held in position, measure with one leg in position.
   e. While holding the knees, pull the footboard against the child's feet. Many babies will point their toes, but the lead anthropometrist should ensure the feet are perpendicular to the back of the board as much as possible.
7. **Upon reading the measurement, the examiner will clearly call out the number to the recorder.** Record the child's length in centimeters to the last completed 0.1 cm. (1.0 mm).
8. Keeping the child in place, release the sliding footboard, and prepare to repeat the measurement. Re-position the child for a second and third measurement.



Measure Standing Height

1. Ensure that the height board is on level ground.
2. Working with the mother, and kneeling in order to be at the level of the child:
    a. Help the child stand on the baseboard with the weight of the child evenly distributed on both feet. The heels of the feet are placed together with both heels touching the base of the vertical board. Place the feet pointed slightly outward at a 60 degree angle.
    b. The back of the head, shoulder blades, buttocks, calves, and heels should all touch the vertical board. Arms should hang freely by the sides of the body with the palms facing the thighs. **Note: Standing with all body parts touching the board may be difficult for some children, in which case, help the child to stand on the board with one or more contact points touching the board.**
    c. Ask the mother to hold the child's knees and ankles to help keep the legs straight and feet flat, with heels and calves touching the vertical board. Ask her to focus the child's attention, soothe the child as needed, and inform you if the child moves out of position.
    d. Position the child's head so that a horizontal line from the ear canal to the lower border of the eye socket runs parallel to the baseboard.
    e. Ask the child to inhale deeply and to stand fully erect without altering the position of the heels. If necessary, push gently on the belly to help the child stand to full height.
    f. Still keeping the head in position, use your other hand to pull down the headboard to rest firmly on top of the head and compress the hair.
3. **Upon reading the measurement, the examiner will clearly call out the number to the recorder.** Record the child's height in centimeters to the last completed 0.1 cm (1.0 mm).
4. Keeping the child in place, release the sliding headboard, and prepare to repeat the measurement. Re-position the child for a second and third measurement.


HEADPIECE FIRMLY ON HEAD
15
HAND ON CHIN
9
SHOULDERS LEVEL
10
LEFT HAND ON KNEES; KNEES TOGETHER AGAINST BOARD
5
RIGHT HAND ON SHINS; HEELS AGAINST BACK AND BASE OF BOARD
4
11 HANDS AT SIDE
E1 ON KNEE
3
ON KNEES
2
1
QUESTIONNAIRE
E2
12
8
LINE OF SIGHT
13
14
BODY FLAT AGAINST BOARD
7
6

Dismantling the ShorrBoard

1) Stand the board upright: face the board and step on the base with one foot to keep it stable.
2) Slide the head/footpiece into the base of the main board.
3) Release the clasp on the back of the extension piece and remove it. Push the clasp FLAT against the extension piece.
4) To attach the extension piece to the main board, turn the front of the extension piece inward and place it against the front of the main board. Make sure that all sides of the extension piece are straight and in line with the main board.
5) Push on the bolt that is on the back of the extension piece and screw it into the main board.
6) Put the board back inside of the carrying case for storage until your next use.

Measuring Weight

The SECA 874 scale will be used to weigh infants and children to the nearest 0.1 kg. Infants and young children can also be weighed simultaneously with their parent or guardian by the unique "mother-baby" function (parent or guardian is weighed and then the infant or child is weighed while held by the parent).

Explain to the mother that we want to weigh her child to see how he or she is growing. If she has a baby or a child who is unable to stand, she will hold the child on the scale. If the child is 2 years or older/can stand alone, the child will be weighed alone.
Children should be wearing only light clothing, no shoes or sandals, no hair ornaments, and no jewelry. Explain that the child needs to remove outer clothing and shoes/sandals in order to obtain an accurate weight. If the baby is wearing a diaper, the diaper should be removed. If any heavy clothes remain on the child, make a note in the *Notes* section.

Seca 874 Scale

1) Remove scale from bag.
2) Be sure that the scale is placed on a flat, hard, even surface. All 4 legs of the scale should make contact with the ground surface, without wobbling. It may be helpful to place a piece of plywood on the ground underneath the scale.
3) When **batt** appears in the display, you should change the batteries. Remove the old batteries and insert 6 new batteries.

Turn the power on the scale when you are ready to begin weighing.

1. **If the child is unable to stand on the scale**, you will use the 2 in 1 weighing function (called *tared* weighing). The **2 in 1** function enables the weight of babies and small children to be determined while an adult holds them.
    a. Identify a suitable area that is flat for horizontal placement of the scale.
    b. Press the start key with no load on the scale. The scale is ready for use when it sets to 0.00.
        i. If necessary, switch the weight display to KG: hold down the 2 in 1 key for about 3 seconds. Press the start key with no load on the scale. Wait until the display shows 0.00.

c. Ask the adult to remove his/her shoes and stand in the middle of the scale without the child. S/he should remove any long garments, as these can cover the display and also lead to variable measurements.
d. After the adult's weight appears on the display, tell him/her to remain standing on the scale. Press the **2 in 1** key to activate the function.
e. The scale stores the weight of the adult and the display returns to zero. When 0.00 and NET appear in the display, hand the child to the adult. The scale will determine the weight of the child. Once the value is stable for about 3 seconds, the weight is measured.
    i. Note: If an adult is very heavy (e.g. more than 100 kg) and the baby's weight is relatively low (e.g. less than 2.5 kg), the baby's weight may not register on the scale. In such cases, have a lighter person hold the baby on the scale.
f. **The positioner will clearly call out the child's weight to the recorder.**
g. Record the child's weight to the nearest 0.01 kg.
h. Repeat the measurement 2 more times. Note that only the baby needs to be removed from the scale; the adult should remain on the scale the entire time.
i. To turn off the **2 in 1** function, press the **2 in 1** key. The **2 in 1** function remains on until you press the **2 in 1** key again, or until the scale switches off automatically.

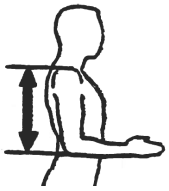
2. **If the child is able to stand on the scale**, you will weigh the child alone. Talk with the child about the need to stand still. Communicate with the child in a sensitive, non-frightening way.
    a. Press the start key with no load on the scale. The scale is ready for use when it sets to 0.00.
    b. Ask the child to stand in the middle of the scale. Once on the scale, the child must stand still. The HOLD function is automatically activated for weights over 1.5 kg/3.3 lbs. The display flashes until a stable weight has been measured. The display is then frozen until the next weighing operation.
        i. Note: If the child jumps on the scale or won't stand still, you will need to use the tared weighing procedure instead.
    c. **The positioner will clearly call out the child's weight to the recorder.** Record the child's weight to the nearest 0.01 kg.
    d. Repeat the measurement 2 more times. Have the child move completely off the scale and then stand again on the scale.

If no further weighing operations are performed, the scale switches off automatically after 2-3 minutes.

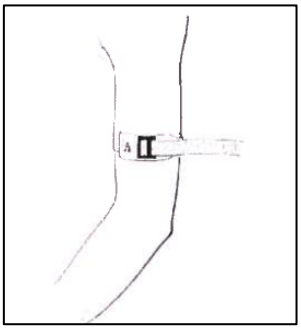
Scale Calibration
In order to monitor the calibration of the scales over time, each team will weigh a 5 kg test weight at the beginning and end of the day.

Measuring Mid-Upper Arm Circumference (MUAC)

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. First, **find the approximate midpoint of the upper arm**. Have the child stand up straight with feet together, and the right arm bent 90 degrees at the elbow, palm facing up. The examiner is positioned behind the child. If it is helpful, mark the midpoint with a permanent marker.
2. To **measure mid-upper arm circumference**, have the child stand up straight with the arms relaxed at the sides. The examiner will stand facing the child's right side. The measuring tape is placed around the upper arm at the marked point.
3. Wrap the tape around the arm, pulling it to lie flat against the surface of the skin. Be careful not to pull the tape too tightly (to compress the skin).
4. The line for reading measurements is clearly labeled on the MUAC tape (READ (cm)). Read the number aligned with the measurement line on the tape. **Upon measuring, the examiner will clearly call out the number to the recorder.** Record to the nearest 0.1 cm (0.1 cm = 1 mm).
5. Keeping the child in place, release the MUAC strip.



3.3. Malaria Rapid Diagnostic Test

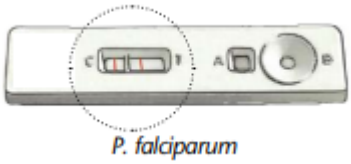
Malaria infection status will be assessed on all enrolled children using a rapid diagnostic test (RDT) at baseline and 8 weeks after admission into the nutritional program. At this point, we will also take the child's temperature.

Supplies

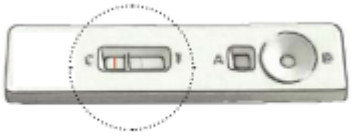
- Mobile data collection device & accessories
- RDT test packet
- Alcohol swabs
- Gloves
- Lancet
- Buffer
- Timer

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.

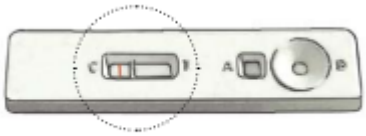


    i. The test is positive even if the line near "T" is faint



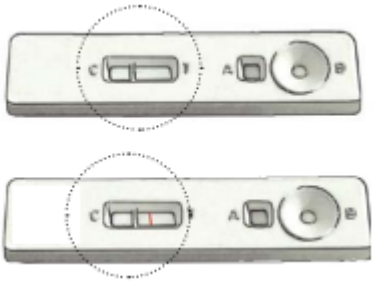
P. falciparum (faint +)

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.

3.4. Rectal swab collection

Rectal swabs will be collected at baseline and at week 8 in a random subset of children.

Procedure

The test will require that the child’s parent and examiners work together to obtain a good sample. Is it important to describe the test to the parent so that they can best assist with keeping the child still during the procedure.

Rectal swabs can be collected in the following way:

1. Put on a clean pair of gloves.
2. Partially open the fecal swab package and remove the top section of the collection vial (this can be discarded).
3. Position the child:
    - Lie the child on his/her back, hold legs in the air (it is useful to have assistance).
    - Or have the child lay on his/her stomach across the mother/guardian’s lap
4. Remove the swab from the package. Take care that the cotton tip is not touched. If it is touched, throw the swab away and begin with a new one.

5. Insert the tip of the swab into the child's anus only as far as needed to contact fecal material (1-3cm) and rotate 180 degrees. The tip should be a brownish color when removed.
6. Place swab into the preservative in the collection tube. Make sure the swab is fully submerged in the liquid preservative and then break the swab off using the pre-scored breaking point.
7. Screw the cap back on the tube and make sure that it's tightened. Wrap the area where the cap meets the tube with Parafilm to ensure that the sample will not leak, and then place the tube into the appropriate sample box.
    - If the swab cannot be broken off while the tip is fully submerged in the liquid, try twirling the swab in the liquid first (to release the contents of the sample into the preservative) before breaking it off. Avoid rubbing the sample on the tip of the swab off on the side of the tube where there is no liquid.
8. Place a random number label on the collection tube.
9. Place the tube the rectal swab container.
10. Swab storage for Genetic analysis: Store samples at room temperature. According to the manufacturer, the preservative in the tube will preserve DNA for 5 months at room temperature (7 days for RNA), and thereafter can be frozen (-20°C or -80°C) for long-term storage.

Materials for Rectal Swab Collection

Swab

An individually-wrapped Copan flocked swab with a plastic shaft will be used to collect the rectal swab and then placed into a Zymo transport medium.

Sample Tube with Media

The specimen will be in a sterile Stool Nucleic Acid Collection and Transport Tube containing Zymo research Transport Medium with a cap that will be tightened firmly.

3.5. Vital Status

Vital status will be recorded at all follow-up visits, including whether the child is alive, has died, or has moved. Date of death and location of move will be recorded.

3.6. 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 or a short course of oral amoxicillin. We will monitor adverse events following treatment as described in Section 5.

Study Medication Description

Zithromax® for oral suspension is supplied in bottles containing azithromycin dehydrate powder equivalent to 1200mg per bottle and the following inactive ingredients: sucrose; tribasic anhydrous sodium phosphate; hydroxypropyl cellulose; xanthan gum; FD&C Red #40; and flavoring including spray dried artificial cherry, crème de vanilla, and banana. After constitution, a 5mL suspension contains 200mg of azithromycin.

The oral amoxicillin routinely used at each CSPS for treatment of uncomplicated severe acute malnutrition will be used for this trial.

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)

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

Oral amoxicillin (80 mg per kilogram of body weight per day, divided into two daily doses) will be administered for 7 days. The first dose will be administered by the study nurse, who will teach the caregiver how to administer the medication at home. The remaining doses will be administered by the caregiver.

Medication Procurement

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

Medication Quality Control

Study medication will be stored at each site prior to use. The CRSN 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

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 study team member conducting the follow-up visit will email the CRSN Principal Investigator, who 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 and the DSMC as needed. Information on all adverse events, serious and non-serious, will recorded on data collection forms through the mobile application.

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- 8. Written informed consent will be collected on paper and the study nurse will record treatment administration on paper. All other data will be collected electronically on mobile devices using the Interviewer mobile application by Survey Solutions. Data to be collected are outlined in Figure 1 and Section 2.5.

6.2. Data Management and Security

Electronic data will be uploaded daily to a secure, password-protected, cloud-based server hosted by Survey Solutions. 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.

No identifiers will be collected electronically. 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 using dashboards created on Survey Solutions web-based platform. 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 CRSN. 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. 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.

Comité d'Ethique du Burkina Faso
The study protocol will be reviewed and granted ethical approval by the Comité d'Ethique du Burkina Faso in Nouna 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. 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 CRSN, and by the DSMC. Serious adverse events will be reported to the DSMC based on the determination of the Medical Monitor. Committee members will monitor any severe or unexpected trend that threatens the safety of study participants. Quarterly progress reports will be submitted to the DSMC. Enrollment progress will be reviewed after 1 month to assess feasibility. Stopping guidelines will be agreed upon prior to the start of the study, and the DSMC will be authorized to end the study if they deem necessary.

9. STATISTICAL METHODS

9.1. Sample Size and Power

Specific Aim 1 We assume that inclusion of 300 children (150 randomized to each arm) will provide 80% power to detect a 27% 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 Niger comparing children receiving amoxicillin to placebo over time.[5] We assumed an average weight gain of 4.9 g/kg/day in the amoxicillin arm, with a standard deviation of 3.9 g/kg/day, and loss to follow-up of 10%. A 27% increase corresponds to a mean difference in weight gain of 1.3 g/kg/day, or an average weight gain of 6.2 g/kg/day in the azithromycin arm.

This calculation was performed in Stata using the following command:

power twomeans 4.9, sd(3.9) alpha(0.05) power(0.8) n(270)

Specific Aim 2. Inclusion of 300 children (150 randomized to each arm) will provide 80% power to detect an 15 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 for uncomplicated SAM in Niger.[5] We assumed that 66% 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 0.66, alpha(0.05) power(0.8) n(270)

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.

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

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

- $e \sim N\ (0, \sigma^2)$

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 CSPS, WHZ, and MUAC.

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REVISIONS HISTORY

- June 4 2020: change inclusion criteria from "Has not been admitted to a nutritional program for the treatment of SAM in the 3 preceding months" to "Has not been admitted to a nutritional program for the treatment of SAM in the 2 preceding weeks"
- June 30 2020: Definition of recovery modified to fit the national program.
- Error in the nutritional recovery number

APPENDIX

Appendix 1. Informed Consent Documents
Appendix 2. Study Forms
Appendix 3. Appetite test
Appendix 4. Standard medical protocol for severe malnutrition