Statistical analysis plan for:
IRAM Chad– Integrated Research on Acute Malnutrition, a clustered randomized controlled trial in Chad

Version 1.0: October 14, 2021

Version 2.0: September 22, 2022

Summary of changes between v1.0 and v2.0:

1- In November 2021, the sponsor agreed to extending the study with two months (3 studies), then, in January 2022, to extend the study on relapse prevention with 3 additional months (see Table 2: Selection of study participants, inclusion and exclusion criteria, sample size and follow-up details for the 3 study cohorts.)

2- We adjusted definition of primary outcomes and indicators creation for cohort 2 (see section 3.4.1 Primary study outcomes, and section 5.2 Creation of variables related to treatment (cohort 2))

Study registration on clinicaltrials.gov (NCT04867694) on April 30, 2021

1 Background

Worldwide, 47 million children under five years of age suffer from wasting [1]. Wasting significantly increases the risk of death: it kills 875,000 children under the age of five per year. All Member States of the World Health Assembly (WHA) have agreed to reduce and maintain the prevalence of wasting to less than 5% by 2025 [3]. However, the prevalence of wasting remains persistently high in many West African countries such as Mali (14.8%), Mauritania (13.5%), Chad (12.9%) and Niger (10.1%). Wasting trends suggest that the WHA goal will not be achieved in these countries, despite their commitment to addressing wasting as expressed in their nutrition policies.

There is an urgent need to test innovative solutions to prevent wasting and increase screening, adoption and adherence to treatment. Options include integrating prevention into screening to increase coverage and prevent wasting; strengthening referral processes for wasted children and supporting and encouraging parents to enroll their children in treatment; establishing outreach screening and treatment units; transferring some treatment responsibilities to community health workers; and/or simplifying treatment procedures for both parents and service providers.

In response to this urgent need, UNICEF and IFPRI started a multi-country partnership to generate evidence on wasting prevention and treatment interventions in four countries: Chad, Mali, Mauritania,

[1] Defined in children aged 0-59 months as a weight-for-height score of less than -2 z-score according to WHO weight-for-height references [5]; depending on the context and the measurement tools used, wasting is also defined by a brachial perimeter of less than 125 mm in a child aged 6-59 months or by the presence of bilateral edema (0-59 months).

and Niger. Several interventions aiming at addressing gaps along the spectrum of wasting will be integrated and implemented at community and health center levels (first and second lines) given their demonstrated importance in the 4 countries of interest.

In Chad, an impact evaluation will be conducted to generate strong evidence on the effectiveness of these integrated interventions to reduce wasting among young children.

2 Study objectives

The overall objective of the study is to assess the impact of an integrated package of interventions covering prevention, early detection, treatment, and relapse prevention on the prevalence of child wasting.

The implementation of the intervention package will be led by the Sahelian Association for Applied Research and Sustainable Development (ASRADD) in collaboration with the health services of the health district of Mongo, Guéra province, and other implementing partners in the area. The activities will take place at the health center and community levels, and include i) a prevention component combining the strengthening of community care groups (who will conduct home visits to deliver behavior change messages) and the distribution of a nutritional supplement (CSB++) to [6-11] months old children diagnosed as non-wasted (as a result of the green MUAC) and water purification inputs to all [6-11] months old children unconditionally (regardless of wasting status); ii) a component related to strengthening screening and referral that will involve families (family MUAC approach), with [6-23] months old children, trained and supervised by community care groups (who will also conduct routine screening); children diagnosed as wasted will be referred and will receive treatment (including food supplements) at the nutritional units (at health center or in the community); iii) a treatment component that includes strengthening the protocol for integrated community management of acute malnutrition (CMAM) currently in use in Chad, as well as support from community groups through follow-up home visits to children with wasting for counseling and verification of adherence and compliance to treatment; and iv) a final relapse prevention component combining a 6-month home follow-up by community care groups for [6-23] months old children who recovered from wasting to provide nutritional counseling, a preventive nutritional supplement (CSB++), water purification inputs, and a supervision of screening by families.

3 Study methods

3.1 Study area and population

The study will be conducted in the health district of Mongo located in the Guéra province, which includes 26 zones of responsibility (ZR) of the health centers (CS). The population statistics of Guéra province show a total of 31,771[2] children aged 6-59 months in 2019 with 12.9 (12.1-13.7) % of them suffering from a weight-for-height <-2 z-score (10).

[2] Projections considering the average household size in Chad of 5.2 individuals according to the 2009 census.

3.2 Study design

We designed a two-arm, cluster-randomized, non-blinded, longitudinal, effectiveness trial to study the impact of the PASIM intervention as compared to the standard of care in the study area. Two study groups will be formed, a control/comparison group, and an intervention group receiving the integrated package of interventions. The activities of the control and intervention group are summarized in Table 1.

Table 1: intervention package in intervention and comparison groups

	Intervention	**Comparison**
Prevention	Integrated community care group (CCG) Weekly home visits: BCC **(pregnancy to 23 mo)** Monthly village-level distribution in presence of CCG volunteer of 360 g of soap + 1 L of bleach + 3 kg of CSB++ **(non wasted 6-11 mo)** MNPs (12-23 mo)	No intervention (some pre-existing CCG with no support since 2019; some areas with punctual preventive interventions)
Screening	Family MUAC (6-23 mo) Integrated CCG (6-23 mo) Weekly home visits: training and supervision of family MUAC, MUAC screening, referral, follow-up on referral through supervisor (NGO promoter)	No intervention (Contact with existing CCG and health system ; some areas with caregivers trained to family MUAC in 2019)
Treatment	Current CMAM protocol (adapted), health center or community site (6-59 mo) SAM/MAM treatment, MUAC only, reduced intensity, culinary demonstrations at community sites Strengthened RUTF/RUSF supply chain Integrated CCG (6-23 mo) Weekly home visits: general and AM specific counselling, ensure RUSF/RUTF compliance Monthly village-level distribution in presence of CCG volunteer of 360 g of soap + 1 L of bleach **(6-23 mo)**	Same as for intervention group Strengthened RUTF/RUSF supply chain No intervention
Relapse prevention	Integrated CCG Weekly home visits: specific counselling on IYCF **(6-23 mo for 6 mo)** Monthly village-level distribution in presence of CCG volunteer of 200 g of soap + 400 mL of bleach + 3 kg of CSB++ **(6-23 mo for 6 mo)**	No intervention

Abbreviation used: BCC, Behavior Change Communication; CCG, Integrated community care group; CMAM, Community-based management of acute malnutrition; CSB++, improved corn-soy-blend for young children; MAM, Moderate wasting; MNPs, Micronutrients powder; MUAC, Mid-upper arm circumference; RUSF, Ready-to-use supplementary food; RUTF, Ready-to-use therapeutic food; SAM, Severe wasting.

In the intervention villages, all households with a pregnant woman and/or a child below 2 years of age will be eligible to be enrolled for follow-up by a community care group member and will receive the intervention components described in Table 1 depending on the child age and nutritional status.

Considering the short time frame to conduct the study, the research is limited to the age group most at risk of wasting. Thus, the target population comprises all [6-23] months old children of the study area, whether healthy, wasted, or recovered from wasting.

We will follow an open cohort (**main cohort**) of children aged 6 to 6.9 months, included for a period of 7 months and followed up monthly until the end of the study; and will assess the overall impact of the intervention on the longitudinal prevalence of wasting, as well as on secondary outcomes (described below in section 3.4).

In addition, we will follow two other cohorts to further study the impact of the intervention in the subgroup of children enrolled for treatment, and in the subgroup of recovered children.

- For the **treatment cohort**, we will use health system records to enroll all children aged 6-23 mo living in the 100 villages of study area and admitted for wasting treatment at a health center or a community site in the Mongo District during the study period. We will follow them from program admission to program exit, using the registers data, and will study the impact on the recovery rate and other secondary outcomes.
- For the **relapse prevention cohort**, we will follow for 6 months a cohort of children aged 6-23 mo who have been treated and have recovered from wasting and will assess the impact of the intervention on the incidence of relapse, as well as on secondary outcomes.

While the main cohort study is an experimental study[3], the treatment cohort and relapse prevention study are quasi-experimental in nature. The quasi-experimental character of these two sub-studies implies the random character of the intervention and comparison group is not fully guaranteed. More precisely, children enrolled in the treatment cohort may not be comparable between study groups because the BCC and food supplement may prevent a proportion of the usual prevalence of wasting. Similarly, a higher screening coverage or screening by family MUAC may refer children with wasting with different characteristics as compared to those in the comparison group. Therefore, any impact or lack of impact of the intervention to support the CMAM services need to be interpreted with caution, as it may be a result of both the intervention and any different characteristics of the enrolled samples of children. For the same reasons, the results of the relapse prevention study must be interpreted bearing in mind possible impacts of the preceding preventive BCC and food supplement and improved screening and referral (studied in the main cohort), as well as possible impacts on the adherence and recovery rates of CMAM services (studied in the treatment cohort).

[3] The main cohort study is an experimental cluster-randomized controlled study that guarantees (if random allocation of clusters is successful) that the samples of children enrolled in the intervention and comparison group have similar household, caregiver, and child characteristics. Therefore, any observed impacts can be exclusively associated with the intervention.

3.3 Randomization

As the intervention is implemented at the village level, and individual randomization was not feasible, the village was used as the unit of randomization (cluster). The main town of Mongo was split into several clusters, which consisted of the administrative districts of Mongo town, as districts had each their own district authorities (similar to village authorities in rural villages) and were attached to various health centers within Mongo town.

For accessibility issues (dispersion of the population in small hamlets) and to increase the probability of finding the necessary number of children each month, only the 100 most populated villages or relevant groupings of neighboring villages (as defined by implementing partners prior to randomization) of the 241 villages in the Mongo Health District were included in the study area. They hosted about 8 out of 10 children in the Health District and were randomized between an intervention and a control group, after stratification to balance village size, and urban/rural status between groups. Specifically, a first level of stratification was based on the criterion of the total population of the village or group of villages. The 50 most populated villages were randomized separately from the 50 least populated villages. A second level of stratification was considered in each subgroup according to the urban/rural status of the health center to which the village was attached.

These 100 clusters were randomly assigned to the intervention and control groups using Stata software by an investigator based in Dakar with no knowledge of the study area. Stata's "sample[4]" command was used to perform a simple random draw of half of the villages within each stratum. The villages randomly selected by the software were assigned to the intervention group and the others to the control group. To ensure the randomness and replicability of this draw, a random seed was obtained from the random number generator on random.org.

3.4 Study outcomes

3.4.1 Primary study outcomes

For this study, wasting will be defined by WHZ<-2 (relative to the WHO reference of 2006) or MUAC<125 mm or bilateral edema. Moderate wasting (MAM) will be defined by -3≤WHZ<-2 (relative to WHO reference of 2006) or 115mm≤MUAC<125 mm. Severe wasting (SAM) will be defined by WHZ<-3 (relative to WHO 2006 reference) or MUAC<115 mm or bilateral edema.

The primary outcomes of the study will be:

1. Longitudinal prevalence of wasting among children enrolled at 6 months of age followed monthly until the end of the study (cohort 1). This indicator is defined for each child as the number of visits during which wasting is observed divided by the total number of monthly visits made (by interviewers).

[4] Gould, W. W. 2012a. Using Stata's random-number generators, part 2: Drawing without replacement. The Stata Blog:

Not Elsewhere Classified. http://blog.stata.com/2012/08/03/using-statas-random-number-generators-part-2-drawing-without-replacement/.

2. The recovery rate in children enrolled at [6-23] months of age for up to 3 months of treatment in a treatment unit and followed through to discharge (cohort 2). This indicator was initially defined in the protocol as the number of discharges considered cured according to national program criteria (WHZ>-2 and MUAC>=125mm and absence of bilateral edema for two consecutive visits, within 12 weeks of enrollment in the program) divided by the total number of exits recorded. Due to COVID-19 modifications in the implementation of the national protocol, children are discharged based on the MUAC criteria only, after only one visit, and WHZ is not measured. We therefore redefined this indicator as the number of discharges with MUAC>=125mm within 12 weeks of enrollment in the program, divided by the total number of exits recorded.
3. The incidence of wasting in children enrolled at [6-23] months of age at discharge from a wasting treatment program and followed for 6 months (Cohort 3). This indicator is defined as the number of new cases of wasting recorded during monthly visits.

3.4.2 Secondary study outcomes

Secondary outcomes of the study include:

For Cohorts 1 and 3 :

- The longitudinal prevalence of :
  - Wasting, defined as above (cohort 3)
  - MAM, defined for each child as the number of MAM diagnoses divided by the total number of monthly visits made
  - SAM, defined for each child as the number of SAM diagnoses divided by the total number of monthly visits made
- The incidence of :
  - Wasting, defined as above (cohort 1).
  - MAM, defined as the number of new MAM cases recorded during monthly visits.
  - SAM, defined as the number of new SAM cases recorded during monthly visits.
- The prevalence of anemia defined as the proportion of children with a hemoglobin level below 11g/dl at the end of the study.
- Mean hemoglobin concentration at the end of the study.
- Prevalence of stunting defined as the proportion of children with HAZ <-2 (relative to the 2006 WHO reference) at the end of the study.
- The average z-scores HAZ at the end of the study.
- Wasting screening coverage defined as the proportion of children screened (using MUAC, weight-for-height or bilateral edema) in the month prior to the monthly visit. Two sub-outcomes will also be considered:
  - Screening coverage by care groups.
  - Screening coverage of the family MUAC component, which is the screening performed by a family member in the past month.
- Linear growth rate defined as the change in height-for-age index per month.
- Speed of weight growth defined as the change in weight-for-height index per month.
- Weight gain defined as the weight change per month.
- MUAC gain defined as the change in MUAC per month.

- The longitudinal prevalence of childhood morbidity, i.e. acute respiratory infections, fever, diarrhea and malaria, defined as the number of reports of signs of these morbidities divided by the total number of days reported (1-3 per monthly visit made).
- Mother/guardian's knowledge of nutrition, WASH, and health expressed as cumulative total and domain scores at exit.
- Infant and young child feeding (IYCF) practices:
  - Introduction of (semi) solid and soft complementary foods .
  - Minimum dietary diversity in children, defined as the proportion of children who consumed at least 5 of the 8 food groups (including breast milk) the day before the survey.
  - Minimum meal frequency for children, defined as the proportion of children who had eaten the day before the survey: 2 meals for breastfed children 6-8 months, 3 meals for breastfed children 9-23 months, or 4 meals for non-breastfed children 6-23 months.
  - Minimum acceptable diet, defined as the proportion of children with both minimal dietary diversity and minimal meal frequency on the day before the survey.
  - Consumption of iron-rich or iron-fortified foods in children.
- Practices related to water, hygiene and sanitation, as per Standard USAID indicators related to drinking water source, treatment, storage; hand washing; and sanitation
- Vaccination coverage, defined as the proportion of children with complete vaccination for their age.

For Cohort 2 [5] :

- Nutritional status (measured by MUAC) at admission in treatment unit.
- The duration of treatment defined as the number of days spent on treatment (between admission and discharge).
- Treatment adherence defined as the proportion of cases enrolled for treatment who received timely treatment from dedicated services until recovery.
- The treatment outcome (drop-out, death, transfer, non-response rates).
- longitudinal prevalence of childhood morbidity defined by the number of days for which signs of these morbidities were reported divided by the total number of days observed/reported in the recall periods.

3.4.3 Auxiliary outcomes

In addition to these study outcomes, the impact of the package on three auxiliary study outcomes will also be assessed in cohort 1 and 3. They are not reported as formal study outcomes because of the imprecision of their estimate or the small size. These outcomes will be considered in an exploratory manner:

[5] All the results cited below will be collected from the registers (including follow-up sheet) of the wasting treatment services (without collecting personal information of mothers/children, such as names, addresses, date of birth, telephone nr.). There will therefore be no data collection from mothers/children attending the consultations.

i) Enrollment of MAM and SAM cases defined as the proportion of cohort 1 or cohort 3 children screened positive in the month prior to the monthly visit (conducted by the survey teams) who were enrolled in a wasting treatment program.

ii) Treatment coverage defined as the proportion of cohort 1 children with SAM and/or MAM under treatment as recalled by the child's caregiver

Results i) and ii) will be strongly influenced, in both study groups, by the MAM/SAM cases referred by the survey teams who will record anthropometry during monthly visits. In the case of SAM, which is a life-threatening condition, the investigators must for ethical reasons refer children from both study groups to the health center to initiate treatment. Thus, the real impact of the intervention on enrollment and treatment coverage may be underestimated.

3.5 Sample Size

3.5.1 Cohort 1 – primary outcome: longitudinal prevalence of wasting

The main cohort (#1) will include 1,750 children in the community aged 6 to 6.9 months, included for a period of 7 months and followed up monthly until the end of the study (total duration: 9 months).

The main cohort (#1) will include children aged 6-6.9 months. Given the small size of most villages and the sample size needed to detect a significant, plausible and meaningful difference in longitudinal wasting prevalence (primary outcome) between groups, we have calculated that we need to include an average of 3 children per month for 7 months in the 50 largest villages (25 villages in the control group and 25 in the intervention group) and an average of 2 children per month for 7 months in the 50 smallest villages in the study area (i.e., the medium-sized villages in the Mongo Health District: equally 25 in the control group and 25 in the intervention group). The children will all leave the cohort in the same month: counting the month of inclusion, the children will be seen for a maximum of 9 months (for children included at the start of the study) and a minimum of 3 months (for children included during the 7th month). This will result in a total sample of 1,750 children (10,500 visits in total of which 1,750 inclusions and 8,750 follow-ups). With 15% dropout**, the size of this study would provide sufficient power to detect a relative decrease of about 35% in the longitudinal prevalence of wasting**, with a power of 80% and a statistical significance of 5%, taking into account the cluster effect at the village level and the imbalance in cluster size.

3.5.2 Cohort 2 - primary outcome: recovery rate

The treatment Cohort (#2) will include all 6-23 months old children living in the 100 study villages and registered for treatment, based on health system records.

Using 2019 health district statistics, the total number of SAM cases (6-23 months of age) over 9 months of follow-up was estimated at 3,928. We assumed the number of MAM cases would be at least as many.

With 100 clusters that each have an average of 78 cases of SAM and MAM over a 9-month period, assuming a recovery rate of 85%, a statistical power of 80%, a type I error of 5% and an intra-cluster coefficient of 0.05, **a minimum difference of ~5 percentage points in the recovery rate could be detected in children aged 6-23 months.**

3.5.3 Cohort 3 - Primary Outcome: incidence of relapse

The relapse prevention cohort (#3) will include 700 [6-23] months old children living in the 100 villages in the study area, who were discharged from treatment and recovered from wasting, and will be followed up monthly for 6 months.

Given the small size of most villages and the required sample size, we have calculated that we need to enroll 8 children in the 50 largest villages and 6 children in the 50 average villages and follow them every month for 6 months each. This will result in a total sample size of 700 children (4,900 visits in total, including 700 inclusions and 4,200 follow-ups). **Such a sample size would provide sufficient power to detect a decrease of about 33% in the incidence of relapse.**

3.6 Sampling and study inclusion criteria

Details on the selection of children, inclusion and exclusion criteria, and changes to the protocol, are given in Table 2.

Table 2: Selection of study participants, inclusion and exclusion criteria, sample size and follow-up details for the 3 study cohorts.

	Main cohort	Treatment cohort	Relapse prevention cohort
Selection of participants	In each village, random selection from a randomly ordered census list of children aged 0-6 months (census conducted by the survey team in the first month of the survey), prepared by an investigator based in Dakar using Stata software. Children not meeting inclusion criteria (see below) will be replaced until the maximum number of children is met (3 times the number of months of inclusion), or until the list of eligible children is exhausted.	All records of children (aged [6-23] months) living in the 100 most populated villages in the study area and admitted during the study in a treatment program by the national CMAM program. Treatment data will be collected by the CMAM treatment units as part of their routine. Each treatment unit will be visited by an enumerator who will be responsible for monitoring data quality and copying anonymous data from the registers to electronic forms.	All available children in each village who will be discharged from CMAM treatment (based on treatment unit registers) and recovered will be invited to participate in the study until the required sample size is reached for each village (8 children). In villages with more children than necessary, the study team will invite children to participate in the order of a randomly ordered list prepared by an investigator based in Dakar using Stata software.
Inclusion criteria	6-6.9 months of age. Child singleton. Resident of the village. Consent of the mother or guardian.	Child admitted for treatment in a national treatment program. 6-23 months of age at admission. Child lives in one of the 100 villages in the study area.	Child has been successfully treated for wasting (defined as MUAC ≥125 mm) and has been discharged from the national treatment program within the last 30 days. 6-23 months of age at inclusion. Child singleton.

	Main cohort	Treatment cohort	Relapse prevention cohort
			Resident of the village. Consent of the mother or guardian.
Exclusion criteria	Congenital malformations that make anthropometric measurements impossible. Mother intends to leave the study area by December 2021.	None.	Congenital malformations that make anthropometric measurements impossible. Mother intends to leave the study area by December 2021.
Sample size	1,750 children	Exhaustive inclusion	700 children
Intended duration of inclusion	7 months	9 months	2 months
Follow-up frequency	Monthly	Bi-monthly visit by enumerators to health center treatment units, and monthly visits to community treatment units.	Monthly
Intended study duration	enrolled children will be followed until the end of the study, with a total study duration of 9 months	from program admission to program exit, with a total study duration of 9 months.	Follow-up of all children for 6 months, with a total study duration of 8 months.
Changes to the protocol	November 2021: Study duration was increased by a month and exits were split evenly across the 2 last months of the study, based on enrollment order.	November 2021: Study duration was increased by a month.	November 2021: To meet the sample size, we extended the inclusion duration to 7 months January 2022: To meet the sample size, we extended the inclusion duration to 9 months, and we released the limitation on the maximum number of children per village. We also extended the total study to 12 months, and enrolled children will be followed-up either for 6 months, or until the end of the study, whatever comes first.

4 Data management

The management of all research data will follow IFPRI's institutional research data management protocol, overseen by the IFPRI Data Governance Committee, as well as UNICEF data governance standards. All received data will be carefully anonymized and de-identified so that the privacy of participants and research subjects is fully protected. Personally Identifiable Information data (PII; names, telephone

numbers, GPS coordinates, date of birth) will be stripped from the research data when receiving the data on the server. During data collection, PII data will be stored in a separate secured server folder accessible only to the Principal Investigators. PII data will only be used to identify a household to conduct additional verification of previously collected data. When data collection and data validation have been completed, PII data will be destroyed.

In accordance with IFPRI's policy on research data management and open access, at the time of publication of scientific articles presenting the primary results, fully anonymized databases will become a public good and will therefore be made available to the scientific community, government, partners.

All data collection is scheduled to start once the study trial is registered on clinicaltrials.gov.

5 Variables creation

5.1 Variables creation for cohorts 1 and 3

Age will be calculated in days counting the number of days between the date of birth and the date of data collection. Date of birth will be collected at enrollment from each child's health booklet and, if not available, from a vaccination card or any other written record. When no written record will be available, date of birth will be estimated by the enumerator using a detailed calendar of local events.

All weight, length and MUAC measurements will be taken in duplicate by a trained enumerator and a trained assistant, and a third measurement will be taken if the difference between the two repeated measurements is >5mm for length and MUAC and >300g for weight. The average of the two closest repeated measurements will be used for the calculation of nutritional status indicators.

The child weight-for-height and height-for-age z-scores will be calculated using the *zscore06* command in Stata (15), which uses the World Health Organization's growth standard (16).

A wasting episode will be defined as follows: it starts when a child is found to be wasted at the monthly survey and ends when a child does not suffer from wasting at one monthly measurement. MAM and SAM episodes will be defined the same way, except that children who qualify as MAM during the SAM recovery process will still be considered SAM and not MAM.

During follow-up visits, we will interview the caregiver about child morbidity (acute respiratory infections, diarrhea, fever, and malaria) over the previous 3 days. Diarrhea will be defined as recall of at least three loose stools in 24 hours, or of stools with blood. Fever (axillary temperature > 37.5^{o}C) will be measured by a thermometer and the history of fever for each of the 3 previous days will also be recalled. The presence of an acute respiratory infection (ARI) in the 3 previous days will be assessed by recalling the specific symptoms associated with ARI (cough, difficulty breathing, rapid breathing, wheezing). The presence of malaria parasites will be checked by enumerators with a rapid diagnostic test for malaria, if body temperature is above 37.5 °C or if the mother reports a fever episode in the child within the last 72 hours.

The hemoglobin concentration will be measured at enrollment and at exit by spectrophotometry using a HemoCue 301 (HemoCue Ltd, Dronfield, UK), using a drop of capillary blood drawn from the child's finger.

Child anemia and severe anemia will be defined by hemoglobin concentrations of less than 11 g.dL-1 and less than 7 g.dL-1 respectively.

Screening will be defined as caregiver recall that MUAC was measured in the target child.

Single treatment coverage will be calculated at individual level on the sub-group of children with wasting and children recovering from wasting, using the formula:

$$single\ coverage = \frac{C_{in} + R_{in}}{C_{in} + R_{in} + C_{out} + R_{out}}$$

where Cin = current wasting, SAM or MAM cases under treatment, Cout = current wasting, SAM or MAM cases not under treatment, Rin= recovering wasting, SAM or MAM cases under treatment, and Rout = recovering wasting, SAM or MAM cases not under treatment. Children with wasting and recovering children will be identified using the anthropometric measures. Recovering children will be defined as children with wasting the previous month but not wasted the current month.

Principal component analysis will be used to generate a household wealth status score (17). We will include household-level data on materials used in housing roofs, floors, and walls, occupational status of the housing, the main source of light, and assets owned by 5 to 95% of the study sample at enrollment. Tertiles of loadings on the principal component with the highest eigenvalue will be used.

5.2 Creation of variables related to treatment (cohort 2)

Recovery from MAM or SAM will be defined as achieving a normal nutritional status (defined as MUAC≥125 mm) within 3 months after treatment admission.

We will calculate adherence as per the national protocol, i.e. treatment consultations are attended every 2 weeks for SAM treatment or 4 weeks for MAM treatment.

Version SAP 2.0: We added 2 definitions for adherence. Definition 2) is same as (1), with a tolerance if the missed consultation was not actually organized by the treatment unit; Definition 3) is same as (2), with a tolerance if the missed consultation(s) corresponded to a shortage of RUTF or RUSF.

We will inspect the registers data and correct any data entry mistake when it does not correspond to the national protocol. Specifically:

- All children who missed 2 consecutive scheduled consultations will be recoded as default, and their follow-up visits will be dropped from the dataset entry and recoded as a new entry following re-admission after default. The first consultation after default will be considered as admission consultation.
- Exit type coded as recovery will be recoded to “mistakenly coded as recovery” when exit MUAC is less than 125 mm.
- Other exit types will be recoded to “recovered” when exit MUAC is 125 mm or more.

6 Statistical analysis

6.1 Guiding principles and analysis strategy

Data will be analyzed on intent-to-treat basis. To allow for an analysis "as randomized" in the presence of missing data, we will impute missing data of the primary outcomes of the longitudinal study using a multiple imputation strategy under the *missing at random* assumption (see section 6.3 below). Data management, data cleaning, and statistical analyses will be done using Stata 17.0 (Statacorp, USA). The statistical significance will be set at 5%. All statistical tests will be two-sided. The analysis of primary study outcomes will not be adjusted for multiple testing (n=3 primary study outcomes) given the data involved represent three distinct experimental and control study samples with each one primary study outcome.

We will present results from non-adjusted and adjusted linear mixed effects regression models.

The non-adjusted models to analyze cohort 1 and 3 data will use *village (cluster)* as a random intercept and sampling stratum as a fixed effect to represent the study design. The non-adjusted models to analyze cohort 2 data will include sampling stratum as a fixed effect and will use a random intercept at the health center level and a random slope at the village level, to account for nesting of villages (clusters) into health centers (where treatment occurs for children from several villages).

In addition, we will conduct adjusted analyses, adjusting for the following variables:

- covariates that appear imbalanced at enrollment (absolute difference >10 pp) and are unlikely to have been impacted by exposure to the intervention before 6 months of age (cohort 1 and 3; virtually no household, parental or sociodemographic child level data collected at admission in cohort 2).
- child sex, and whether child was the first live birth, since a recent meta-analysis has reported that imbalance in child nutritional status between study groups can be associated to the imbalance in child sex and primiparity (3) (all adjusted models, except that data on first live birth are missing for cohort 2).
- month of enrollment (longitudinal models, cohorts 1 and 3) or month of admission into treatment (cohort 2).
- Child age at enrollment (cohort 3; constant in cohort 1; not detailed in MAM treatment registers used for cohort 2).
- type of nutrition unit where the child is/was treated (cohorts 2 and 3).

6.2 Enrollment characteristics

6.2.1 Characteristics of study groups at enrollment

The presentation of enrollment characteristics (see Table 3) will be done as follows:

- Categorical variables: frequencies and percentages, as appropriate. Percentages will be calculated based on the number of participants for whom data are available.
- Continuous variables: mean and SD or median and interquartile range, as appropriate.

Following the CONSORT guidelines, we will not statistically test for differences between study groups at enrollment in cohort 1 (18). Imbalance will be considered for absolute differences >10 pp (binary

outcomes) or >10 % (continuous outcomes). However, as the intervention risks impacting the size and characteristics of the study population for cohort 3 (if it impacts who is wasted, and then treated and cured from wasting), we will test baseline differences across groups in cohort 3, using linear (continuous outcomes) and linear probability (binary outcomes) mixed-effects regression models with robust estimation of standard errors, considering the cluster as a random effect, and strata and intervention as a fixed effect.

Table 3: Enrollment characteristics for cohorts 1 and 3

Characteristics	**Comments/References**
Household level	
HH size (mean/SD)	
Number of under 5 children in household (mean/SD)	
Number of adults (15-64 y) (mean/SD)	
Polygamous HH(%)	
HH food insecurity (mean and proportion of food secure HH)	Coates J, Swindale A, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for measurement of food access: indicator guide. Washington, DC: FANTA; 2007. https://doi.org/10.1007/s13398-014-0173-7.2
SES status classification (tertiles, %)	Principal component analysis will be used to construct a proxy household Socio-Economic Score (SES) using ownership of various assets (an asset is excluded if ownership is below 5% or above 95% on HH level), housing materials, primary source of lighting, primary energy source, and home ownership. Tertiles of the first principal component (i.e., the one with the highest eigenvalue) will be used.
Improved water treatment technologies used (%)	USAID (2021) Water and development- Indicator handbook. Washington DC
Improved sanitation facility (%)	USAID (2021) Water and development- Indicator handbook. Washington DC
Handwashing station with soap available (%)	USAID (2021) Water and development- Indicator handbook. Washington DC
Improved primary water source (%)	USAID (2021) Water and development- Indicator handbook. Washington DC
Distance to nearest health center, km	Linear distance between households and the nearest health center calculated using Global Position System coordinates
Distance to nearest wasting treatment unit, km	Linear distance between households and the nearest wasting treatment unit (health center or treatment unit in the community)
Household head level	
Male head of household (%)	
Adult (15-64 years) (%)	
Elderly (65+ years) (%)	
Paternal level	
Father is head of HH (%)	

Characteristics	Comments/References
Age (mean/SD)	
Male (%)	
Head of household school attendance	
Has an income generating activity (%)	
Parental confidence scale	Črnčec R, Barnett B, Matthey S. Development of an instrument to assess perceived self-efficacy in the parents of infants. Res Nurs Health. Res Nurs Health; 2008
Severe clinical range (less than 31)	
Moderate clinical range (31-35)	
Maternal	
Biological mother (%)	
Age (mean/SD)	
Spouse of head of household (%)	
School attendance (Never attended school, %)	
Has an income generating activity (%)	
Height (meand/SD)	
Possible depression (EPDS≥10)	Cox JL, Chapman G, Murray D, Jones P. Validation of the Edinburgh postnatal depression scale (EPDS) in non-postnatal women. J Affect Disord; 1996;39:185–9.
Parental confidence scale	Črnčec R, Barnett B, Matthey S. Development of an instrument to assess perceived self-efficacy in the parents of infants. Res Nurs Health. Res Nurs Health; 2008; 31:442–53.
Severe clinical range (less than 31)	
Moderate clinical range (31-35)	
Number of food groups consumed over last 24h (mean/SD)	Out of a maximum of 10 food groups as proposed by Martin-Prevel Y, Allemand P, Wiesmann D, Arimond M, Ballard T, Deitchler M, et al. Moving forward on choosing a standard operational indicator of women's dietary diversity. Rome: FAO; 2015. Food groups are starchy staple foods, nuts and seeds, flesh foods, dark green leafy vegetables, pulses, dairy, eggs, vitamin A rich fruits and vegetables, other vegetables and other fruits
Minimum dietary diversity (having consumed at least 5 of 10 food groups during the last 24h)	Martin-Prevel Y, Allemand P, Wiesmann D, Arimond M, Ballard T, Deitchler M, et al. Moving forward on choosing a standard operational indicator of women's dietary diversity. Rome: FAO; 2015
Body Mass index (kg.m-2) (mean/SD)	
Underweight (BMI<18.5) (mean/SD)	

Characteristics	Comments/References
Assisted delivery of last pregnancy (%)	
Number of antenatal consultations attended during last pregnancy (%)	
Breastfeeding, complementary feeding, health and hygiene, MUAC screening, CMAM knowledge score (mean/SD)	Self-developed questionnaire based on training curricula for GSAN. Mean scores are presented by domain, as well as an overall score based on the 36 questions
Child	
Age (mean/SD)	
Male (%)	
Primiparity	
Introduction of (semi)solid and soft foods (%)	
Minimum dietary diversity (%)	Indicators for assessing infant and young child feeding practices: definitions and measurement methods. Geneva: World Health Organization and the United Nations Children's Fund (UNICEF), 2021
Minimum meal frequency(%)	
Minimum acceptable diet(%)	
Consumption of iron-rich or iron-fortified foods (%)	
Hemoglobin concentration (hb) (%)	As measured by hemocue 301
Anemia (hb<11 g/dl)	
Severe anemia (hb<7 g/dl)	
Weight-for-length Z-score (mean/SD)	Relative to WHO 2006 growth reference
MUAC (mean/SD)	
Wasting (WLZ<-2 or MUAC<125mm or edema)	
Severe Acute malnutrition (WLZ<-3 or MUAC<115mm or edema)	
Length-for-age Z-score (mean/SD	Relative to WHO 2006 growth reference
Stunting (LAZ<-2)	
Weight-for-age Z-score (mean/SD	Relative to WHO 2006 growth reference
Underweight (WAZ<-2)	

6.2.2 Specific considerations on the use of enrollment data

Children will be enrolled in the cohort 1 at the age of 6 months, when the program foresees MUAC screening measurements and inputs distribution to start. However, community care groups in the intervention study arms are tasked to conduct home visits to pregnant and lactating women and caregivers of children up to 24 months of age to provide BCC on child nutrition, health and WASH.

Therefore, it is likely that caregivers with children of 6 months enrolled in the cohort after the start of the program have been exposed to BCC prior to study inclusion in the intervention group. Similarly, it is likely that children enrolled in cohort 3 after the start of the program have been exposed to BCC, MUAC screening or inputs distribution prior to study inclusion in the intervention group. For this reason, all longitudinal analyses of cohort 1 and cohort 3 data will include the data at enrollment as impact data, an analyses studying impacts at exit will not control for enrollment value of the outcome. For study outcomes related to activities that only start between the age of 6 and 7 months, like MUAC-based screening and the distribution of inputs, we will consider data related to the program's impact from the child age of 7 months onwards.

6.3 Treatment of missing data for primary study outcomes

For cohort 1 and 3, we will conduct multiple imputation of missing longitudinal anthropometric data using chained regressions (Stata: mi impute chained (regress)) which imputes missing values under the missing at random assumption[6]. Imputation variables will be the wide-form anthropometric measurements and child age, and complete predictors (independent variables) will be child sex and randomization stratum. We will use 50 imputations (Stata: *add*) with 10 iterations within imputation (Stata: *burnin*) to allow for convergence to a stationary distribution before the imputation. We will inspect imputation quality using trace plots by iteration to assess convergence and box plots to compare distributions of observed and imputed values. In addition, we will examine the fit of imputed child length values along the growth curves.

6.4 Impact assessments

6.4.1 Main analyses

Impact on wasting longitudinal prevalence (primary outcome of cohort 1), wasting incidence (primary outcome of cohort 3), MAM and SAM longitudinal prevalence and incidence, and morbidity longitudinal prevalence, will be estimated using a mixed effects Poisson regression model with robust estimation of standard errors.

For other longitudinal outcomes, we will use linear mixed-effects regression models to assess the impact of the intervention on continuous outcomes and linear probability mixed-effects regression models with robust estimation of standard errors to assess the impact of the intervention on binary outcomes (19). Repeated visits within a child in longitudinal models will be accounted for by including a random intercept at the child level and a random slope at the visit level (defined as number of months since enrollment). For longitudinal models with continuous anthropometric outcomes (growth curves analyses), we will assess if the addition of a quadratic term of time (visit) improves the model fit significantly by applying a likelihood ratio test comparing the model with and without the quadratic term. To assess the specific

[6] De Silva AP, Moreno-Betancur M, De Livera AM, Lee KJ, Simpson JA. (2017) A comparison of multiple imputation methods for handling missing values in longitudinal data in the presence of a time-varying covariate with a non-linear association with time: A simulation study. BMC Med Res Methodol; 17:1–11

impact of the intervention from enrollment at the age of 6 months to the end of follow-up, we will assess the interaction between intervention allocation and time (visit).

For cross-sectional analyses on outcomes measured at exit from cohorts 1 and 3 (mainly cumulative outcomes such as knowledge, vaccination, stunting, etc…) and on cohort 2 outcomes, we will use linear probability mixed-effects regression models with robust estimation of standard errors to assess the impact of the intervention on binary outcomes (including recovery rate, primary outcome of cohort 2), and linear mixed-effects regression models to assess impacts on continuous outcomes (19).

6.4.2 Sub-group analyses

For cohort 1 and 3 data, we will conduct exploratory subgroup analysis of treatment coverage on the sub-group of children with wasting and children recovering from wasting.

For cohort 2 data, we will conduct exploratory subgroup analyses by type of treatment unit, because two distinct treatment protocols are used in Chad for SAM and MAM, and within MAM treatment, implementation strategies are different between the health center platform and the community platform, including the use of two distinct treatment products. These analyses may help explain wasting treatment outcome results.

6.4.3 Sensitivity analyses

We will assess whether impacts on primary outcomes in cohort 1 and 3 are sensitive to the definition of wasting, by assessing impact on wasting prevalence and incidence when wasting is defined with 2 alternative definitions: 1) MUAC < 125 mm or oedema, and 2) WLZ < -2 Z-scores or oedema.

The data from cohort 1 and 3 will be pooled to assess the impact of the intervention on the longitudinal prevalence and secondary study outcomes and incidence of wasting with a larger statistical power. The cohort will be considered a strata and added in all models as a fixed effect.

6.4.4 Secondary analyses of effect modification

Studying effect modification of an intervention offers important insights in the mechanism of a possible impact. In this study, we will assess possible effect modification of the intervention by enrollment characteristic. Given that these tests are explorative in nature, we will assess interaction terms with study group allocation at a statistical significance set at 10%. Statistical models will be the same as described in earlier sections. Results from both adjusted and non-adjusted regression models will be presented. If there are indications of effect modification by one or more covariates, we will present impact results stratified by stratum.