| CLINICAL AND OPERATIONAL RESEACH PLATFORM (CORAL) | OptiMA-RDC Clinical Trial | |
|---|---|---|
| Inserm ALIMA | Version | |
| STATISTICAL ANALYSIS PLAN NCT03751475 | *1.0* | 2020/06/22 |

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**OptiMA-RDC Clinical Trial**

An individually randomized community-based non-inferiority controlled trial comparing the OptiMA nutrition strategy to the standard nutrition protocol effective in Kasai province in the Democratic Republic of Congo in children aged 6-59 months.

| EVOLUTION | | |
|---|---|---|
| **Version/ date** | | |
| 1.0 | 2020/06/22 | Creation |
| | | |

**ABBREVIATIONS**

| | |
|---|---|
| AM | Acute Malnutrition |
| CMG | Methods and management centre |
| DRC | the Democratic Republic of Congo |
| HAZ | Height for Age z score |
| INSERM | National Institute of Health and Medical Research in France |
| MUAC | Mid-Upper Arm Circumference |
| OptiMA | Optimizing treatment for Acute Malnutrition |
| PCIMA | Integrated Management of Acute Malnutrition |
| RUTF | Ready-To-Use Therapeutic food |
| SAM | Severe Acute Malnutrition |
| SD | Standard deviation |
| UNTA | Nutritional Therapeutic Ambulatory Unit |
| UNTI | Internal Nutritional Therapeutic Unit |
| WFA | Weight for Age z score |
| WHZ | Weight for Height z score |

**TABLES AND FIGURE**

# 1 SYNOPSIS

## 1.1 OBJECTIVES

### Principal objective

The principal objective is to determine, 6 months after inclusion, whether the OptiMA strategy, which adapts RUTF dosage according to MUAC and weight in wasted and uncomplicated children 6-59 months of age with bipedal oedema or a MUAC < 125 mm, provides a success rate that is non-inferior to that of the standard DRC protocol in use in the same outpatient health facilities.

### Main secondary objective

The main secondary objective is to determine whether the recovery rate of uncomplicated severely wasted children according to the current World Health Organization (WHO) definition (24) (MUAC <115 mm or WHZ<-3 standard deviation (SD) Z-score or bilateral oedema) managed according to the OptiMA strategy is not inferior to that of the national standard protocol.

### Other secondary objectives

1. Describe and compare the number of RUTF prescribed per child recovered and per child meeting the criteria for "success" between the two strategies.
2. Describe and compare the cost of RUTF treatment per child recovered and per child meeting the criteria for "success"between the two strategies.
3. Describe and compare the relapse proportion to a new episode of acute malnutrition in children who recovered after RUTF treatment with RUTF for each strategy and look for associated factors.
4. Assess whether standard performance indicators of a nutrition program are achieved in the OptiMA arm and compare standard performance indicators of a nutrition program in SAM participants between the two strategies.
5. Describe the anthropometric evolution of children not receiving nutritional supplementation with RUTF when included in the standard protocol.
6. Describe the anthropometric evolution of children with acute malnutrition associated with severe or moderate stunting in both arms.
7. Describe the anthropometric and clinical characteristics of children hospitalized during follow-up.
8. Identify opportunities and barriers to the administration of RUTF treatment.
9. Describe and analyse caregivers' perceptions of the implementation of the OptiMA strategy compared to the actual standard protocol.

## 1.2 METHODS

### Design

This study is a non-inferiority individually randomized-controlled clinical trial conducted at health centre and community level. Participants are randomly assigned to either the OptiMA strategy arm (intervention = OptiMA) or the national standard protocol arm (control = Standard).

**Treatment**

The trial compares two nutritional strategies for management of children with acute malnutrition defined as MUAC <125 mm or WHZ <-3 SD or bipedal oedema: the standard protocol strategy in DRC or PCIMA (standard arm) and the OptiMA strategy (intervention arm).

The differences between the two strategies are (see Table 1):

- Eligibility criteria for treatment with RUTF;
- Average daily nutritional intake;
- The principle of calculating mean nutrient intake;
- Criteria for stopping RUTF.

It should be noted that the other aspects of management (systematic treatment, treatment of other pathologies and medical complications, hospitalisation referral criteria, frequency of visits) are similar to the standard protocol in force in the country (i.e. PCIMA-DRC).

Table 1 : Wasting definition, treatment products, calculation of dosage and recovery definition in the DRC national and OptiMA protocol

| | **National DRC Protocol** | | **OptiMA Protocol** | | |
|---|---|---|---|---|---|
| | **SAM** | **MAM** | **Acute malnutrition** | | |
| **Wasting definition** | MUAC<115mm<br>Or WHZ<-3 (SD)<br>Or Bipedal oedema | MUAC [115mm-124]<br>Or -3 < WHZ <-2 | MUAC < 125mm<br>Or Bipedal oedema | | |
| **Treatment product** | RUTF<br>150-200 Kcal/kg/d | Super cereal plus 200 g/d (~1000Kcal/d)<br>Or<br>RUSF, one 92g sachet /d (500Kacl/d) | MUAC < 115 mm<br>Or bipedal oedema | MUAC [115-119 mm] | MUAC [120-124 mm] |
| | | | RUTF<br>170-200<br>(Kcal/Kg/d) | RUTF<br>125-190<br>(Kcal/Kg/d) | RUTF<br>50-166<br>(Kcal/Kg/d) |
| **Calculation of dosage** | According to weight | Fixed amount, regardless of weight or MUAC status | According to MUAC status and weight | | |
| **Recovery definition** | MUAC≥125mm Or WHZ ≥-1.5 Z score | MUAC≥125mm Or WHZ ≥-1.5 Z score<br>If After recovery from SAM:<br>MUAC≥125mm And WHZ ≥-1.5 Z score<br>And discharge after 3 months. | MUAC≥125mm<br>for two consecutive weeks | | |
| | No oedema for two consecutive weeks | | No oedema for two consecutive weeks and Minimum 4 weeks in program and good clinical health | | |

In the Intervention arm (OptiMA), all children with MUAC < 125 mm or nutritional oedema will be treated with RUTF, according to a new dosing table based on changes in MUAC and weight. The prescribed dosage of RUTF is gradually reduced as weight and MUAC increase.

In the Standard arm (effective standard protocol), children with MUAC < 115 mm or WHZ<-3 SD or nutritional oedema will be treated with RUTF according to the national weight-based protocol dosing table at each visit.

**Table 2: RUTF ration per week according to Standard and OptiMA strategy**

| **Standard RUTF ration per week** | | **OptiMA RUTF ration per week** | | | |
|---|---|---|---|---|---|
| | **MUAC <115 or oedema or WHZ < -3 SD** | | **MUAC < 115 mm or oedema** | **MUAC [115-119 mm]** | **MUAC >=120 mm** |
| **Weight (KG)** | **Number of RUTF sachet per week** | **Weight (KG)** | **Number of RUTF sachet per week** | | |
| **3.0-3.4** | 9 | **3.0-3.4** | 10 | 8 | 7 |
| **3.5 - 4.9** | 11 | **3.5 - 4.0** | 11 | 8 | 7 |
| | | **4.1 - 4.4** | 12 | 9 | 7 |
| | | **4.5 - 4.9** | 13 | 10 | 7 |
| **5.0 - 6.9** | 14 | **5.0 - 5.4** | 14 | 11 | 7 |
| | | **5.5 - 5.9** | 15 | 12 | 7 |
| | | **6.0 - 6.4** | 16 | 12 | 7 |
| | | **6.5 - 6.9** | 17 | 13 | 7 |
| **7.0 - 9.9** | 21 | **7.0 -7.4** | 18 | 13 | 8 |
| | | **7.5 - 7.9** | 19 | 14 | 8 |
| | | **8.0 - 8.4** | 20 | 15 | 9 |
| | | **8.5 - 8.9** | 22 | 15 | 9 |
| | | **9.0 - 9.4** | 23 | 16 | 9 |
| | | **9.5 - 9.9** | 24 | 17 | 9 |
| **10.0 - 14.9** | 28 | **10.0 - 10.4** | 25 | 18 | 10 |
| | | **10.5 - 10.9** | 26 | 19 | 10 |
| | | **11.0 -11.4** | 27 | 20 | 10 |
| | | **11.5 - 11.9** | 29 | 21 | 10 |
| | | **12.0 - 12.4** | 30 | 22 | 11 |
| | | **12.5 - 12.9** | 31 | 22 | 11 |
| | | **13.0 - 13.4** | 33 | 23 | 12 |
| | | **13.5 - 13.9** | 34 | 24 | 12 |
| | | **14.0 - 14.4** | 35 | 25 | 12 |
| | | **14.5 -14.9** | 36 | 26 | 13 |
| **15.0 - 19.9** | 35 | **15.0 - 15.4** | 36 | 28 | 14 |
| | | **15.5 - 15.9** | 36 | 28 | 14 |
| | | **16.0 - 16.4** | 36 | 28 | 14 |
| | | **16.5 - 16.9** | 36 | 28 | 14 |
| | | **17.0 - 17.4** | 36 | 28 | 14 |
| | | **17.5 - 17.9** | 36 | 28 | 14 |
| | | **18.0 - 18.4** | 36 | 28 | 14 |
| | | **18.5 - 18.9** | 36 | 28 | 14 |

| | | | | |
|---|---|---|---|---|
| | **19.0 - 19.4** | 36 | 28 | 14 |
| | **19.5 - 19.9** | 36 | 28 | 14 |

**Study schedule**

- July 2018 to June 2019: Preparation phase.
- July 2019 to January 2020: Inclusion phase of study participants.
- July 2019 to September 2020: Study participant follow-up phase.
- October 2020 to December 2020: Data analysis and dissemination of results.

## 1.3 ELIGIBILITY

**Inclusion criteria**

- Be between 6 and 59 months old
- Meet one of the acute malnutrition criteria defined as follows:
    - MUAC < 125mm or
    - WHZ <-3 SD (WHO standard) or
    - Bipedal Oedema
- Be a resident in the health area where the active screening session takes place
- Have the free, informed, and signed consent of the child's mother or guardian

**Exclusion criteria**

- Children with medical complication requiring hospitalization or negative appetite test or oedema grade +++
- Children allergic to milk, peanuts and/or RUTFs
- Children suffering from a known chronic pathology such as sickle cell anaemia, trisomy 21, congenital heart disease, neurological condition
- Children currently in a malnutrition programme

## 1.4 OUTCOMES

**Primary outcome**

The primary outcome is judged by a binary composite indicator. Children classified as 'success' fulfil all of the following criteria: alive, not acutely malnourished per the definition applied at inclusion and no additional episode of acute malnutrition (inclusion criteria) throughout the 6-month observation period. All other children are classified unsuccessful.

**Main Secondary outcome**

The main secondary outcome will be determined among children in both arms of the trial who fulfil the current WHO definition of SAM. For this sub-group, recovery is defined after a 4-week minimum duration of treatment as clinically well, i.e. axillary temperature <37.5°C, absence of bipedal oedema and for the OptiMA arm a MUAC $\geq$ 125 mm or for the standard arm MUAC $\geq$125 mm or WHZ $\geq$-1.5Z.

**Other Secondary outcomes**

1. The average number of RUTF sachets per child recovered and per child successfully treated.

2. The average number of successful and cured children for a given amount of RUTF.
3. The proportion of relapse to a new episode of acute malnutrition in children who are cured after RUTF treatment.
4. The standard performance indicators of a nutrition program for both arms (i.e. cure rate > 75%, mortality rate < 5%, drop-out rate < 15%, average length of stay in outpatient care, weight gain and average MUAC gain);
5. Median of anthropometric indices (MUAC, WHZ, HAZ, WAZ), proportion of oedema at V0, M3, M6 in children not eligible for RUTF at V0.
6. Success rate and recovery rate of children who combine HAZ <-2 SD and MUAC <125 mm or HAZ<-2 SD and WHZ<-3 SD at inclusion compared to children with HAZ >-2 SD and a MUAC < 125 mm or a HAZ >-2 SD and a WHZ >-3 SD at inclusion.

### 1.5 SAMPLE SIZE

For the main objective: the expected success rate (as defined in paragraph 1.4.1) is 55%.
For the secondary priority objective: the expected cure rate (as defined in paragraph 1.4.2) is 85%.
For both objectives, the margin of non-inferiority set is 10% with a level of significance set at 2.5% unilaterally and a statistical power set at 80%.
The number of randomized subjects required is:
- 772 participants to meet the main objective;
- 414 participants with severe acute malnutrition to meet the secondary priority objective.
We add an inflation factor of 15% for non-exploitable data to the sample size required for each objective because the study takes place in a context with volatile insecurity, recent population displacements, and barriers to access to health structures (geographic, flooding, military, etc):
- 772 x 1.15= 887.8 i.e. 890 subjects to be randomized to meet the main objective or 445/arm;
- 414 x 1.15 = 476.1 i.e. 480 subjects to be randomized in the stratum of severe cases to meet the secondary priority objective or 240/arm.
Once the sample size is reached for the primary objective, we continued to randomise only children with nutritional oedema or MUAC <115 mm or WHZ <-3 Z score (i.e. severe cases according to the WHO definition) until we reached 480 randomised children (i.e. 240 per arm) in this sub-category.

### 1.6 RANDOMIZATION

The randomization list was drawn up by the statistician of the Methodology and Management Centre (CMG) of INSERM, based in Bordeaux before the start of the trial. The numbers of the two arms of the trial were balanced with a ratio of 1:1. The randomisation was stratified by health area and the indices defining children suffering from severe acute malnutrition according to the WHO definition. This double stratification allowed for comparable children per randomization arm in terms of SAM and no SAM characteristics of participants, and for randomizing at the same time in each health area. Randomization is carried out in blocks. Block sizes are kept confidential. Each list is independent of the others, allowing simultaneous randomization across multiple sites. A health area corresponds to a site. The confidential list was integrated into a randomization software program, which was itself integrated into the study's computerized data entry tool. This software allocates a treatment arm by sequentially drawing from this list each time a randomization procedure is completed.

**NON-RANDOMIZED PARTICIPANTS**

Two categories of children included in the trial are not eligible for randomization:
- Children with WHZ <- 3 and MUAC >125mm with no oedema; these children are routinely managed according to the standard protocol. We are including them in the study in order to count them;
- Children with a sibling already included in the study; these children follow the protocol of the already randomized sibling.

## 1.7 RECRUTEMENT STRATEGY

Active screening for acute malnutrition is organized on a monthly basis in the villages of the health areas included in the trial throughout the recruitment phase. During these sessions, health community workers under the supervision of a nurse check the age, MUAC, oedema, weight and height of children aged 6 to 59 months. The WHZ of each child is calculated according to PECIMA national guideline. Children with a MUAC <125 mm or the presence of oedema (grade 1 and 2) or WHZ <-3 are referred to the research nurse in the community health centre for an inclusion visit.
As part of the routine passive screening for acute malnutrition taking place in the health centres included in the study, children aged 6-59 months, residing in the health area and presenting with a MUAC <125 or the presence of oedema or WHZ <-3 are referred to the research nurse for an inclusion visit.
In both cases, caregivers of children meeting the study inclusion criteria receive information about the study and a proposal to participate in the study. After signing the consent to participate in the study and if the child meets the criteria for randomization then the child is randomly assigned to either the OptiMA arm or the standard arm.

## 1.8 FOLLOW UP

Included subjects supplemented by RUTF have a weekly medical and nutritional follow-up at the health centre or UNTA until the end of nutritional treatment (or bi-weekly for children living in villages more than 14km away from the health centre). Subjects who are not supplemented with RUTF either upon inclusion or after RUTF treatment have anthropometric and clinical follow-up every two weeks in their village.
It should be noted that in this trial, the course of care varies according to the anthropometric status of the participant and his or her RUTF treatment according to the eligibility and discontinuation criteria for each arm. As a result, there is not a standard course of care common to all participants. Some participants will be followed only in their village, others will be followed successively at the health centre and then in their village or vice versa. If the participant is hospitalized during his or her follow-up in the study, the periods of hospitalization during the follow-up will be deducted from the follow-up period in the UNTA or in the village. The total duration of follow-up is 6 completed months (M6) after the inclusion visit (V0) for all children included in the trial.

**Figure 1: Schedule of enrolment, interventions and assessments OptiMA-DRC overview**

| | | STUDY PERIOD | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | | | | | Close-out |
| **TIMEPOINT** | | d0 | $m_1$ | $m_2$ | $m_3$ | $m_4$ | $m_5$ | $m_6$ | $m_6$ |
| **ENROLMENT:** | | | | | | | | | |
| **Eligibility screening*** | X | | | | | | | | |
| | | **Outpatient** ⟷ | | | | | | | |
| **Informed consent** | | X | | | | | | | |
| **Allocation** | | X | | | | | | | |
| **INTERVENTIONS:** | | X | **Outpatient or home visits **** ⟷ | | | | | | |
| **Standard strategy** | | X | X | X | X | X | X | X | |
| **OptiMA strategy** | | X | X | X | X | X | X | X | |
| **ASSESSMENTS:** | | | | | | | | | |
| **Clinical examination** | | X | X | X | X | X | X | X | X |
| **Anthropometry measurements** | X | X | X | X | X | X | X | X | X |
| | | | **Inpatient wards** ⟷ | | | | | | |
| **Hospitalization if required** | | | X | X | X | X | X | X | X |

d=day; m=month

*Monthly active screening in 60 villages and passive screening during outpatient visit in 4 health centre

**Weekly (for those living in villages at 14 km or less from the health centre) or bimonthly (for those living in villages more than 14 km from the health centre) outpatient visits at health centre for participants with RUTF supplementation

*** Bimonthly home visits for children without RUTF supplementation.

## 2 STATISTICAL GENERALITIES

### 2.1 MAIN ANALYSIS

**General principles**

The occurrence of the primary endpoint (success rate, defined in section 1.4.1) will be compared between the two-randomization strategies (OptiMA strategy and standard reference strategy). The analyses will not be stratified according to the two-randomisation stratification variables. Stratification of the randomization on the health centre was carried out for logistical reasons and not because heterogeneous results between centres were expected. Stratification of randomization on severity was performed to allow the analysis of the main secondary endpoint. But the analysis of the primary endpoint will be performed on the entire

population of children recruited in the study, hence this analysis will not be stratified on severity. Stratification of randomization on severity was performed to analyse the main secondary endpoint.

The occurrence of the primary secondary endpoint (cure rate in the severe stratum, defined in section 1.4.2) will be compared between the two randomization strategies (OptiMA and standard), for patients randomized in the severe acute non-malnourished stratum

These two comparisons will be made on an "intention to treat [ITT]" basis (including all randomized participants), and on a "per-protocol [PP]" basis (including only those participants who received the full randomized treatment strategy).

The primary analysis (success in the overall population regardless of the level of malnutrition) and the main secondary analysis (cure rate in the "severely malnourished" stratum) in TTI and PP are non-inferiority analyses.

The OptiMA strategy will be deemed non-inferior to the standard strategy if the primary and main secondary analysis statistically demonstrate non-inferiority in both ITT and PP.

The primary analyses in terms of success and recovery will be performed on available data. In case of missing data, a sensitivity analysis will be performed using the maximum bias method. Missing data can be vital status if the child is absent at the last visit, and anthropometric data (weight, MUAC, height). In the case of missing height data, the last available height can be taken into consideration given the low variability of this value from one month to the next.

Participants, who die, withdraw their consent, are transferred to another structure, or are lost to follow-up, will be considered as systematically failing regardless of the treatment allocated and received.

The analysis of certain secondary judgment criteria will be performed for the entire population only in the OptiMA arm, as it would not be calculable in the standard arm. Comparisons will be made only between "severe acute malnourished" participants.

**Decision rules for non-inferiority comparisons**

The OptiMA strategy will be considered not inferior to the reference strategy:

- If the upper bound of the two-sided 95% confidence interval of the difference "success rate in the reference strategy - success rate in the OptiMA strategy" is less than 10% (one-sided test, $\alpha$ =2.5%, 1-$\beta$=80%) in the PP analysis and in the ITT analysis for the main objective,
- And if the upper bound of the two-sided 95% confidence interval of the difference "cure rate in the reference strategy - cure rate in the OptiMA strategy" is less than 10% (one-sided test, $\alpha$ =2.5%, 1-$\beta$=80%) in the PP analysis and in the ITT analysis for the priority secondary objective.

If non-inferiority is demonstrated, the other secondary analyses will be performed, and if appropriate, in the superiority analysis. The OptiMA strategy will be concluded to be superior to the reference strategy if the OptiMA strategy is judged to be non-inferior to the reference strategy), and if it is superior to the reference strategy for one or more secondary endpoints.

If the non-inferiority of the OptiMA strategy is verified, then we can askwhether the Optima strategy is superior. The OptiMA strategy will be considered superior to the standard strategy if the upper bound of the two-sided 95% confidence interval of the difference "success rate in the reference strategy - success rate in the OptiMA strategy" is greater than 0% (one-sided test, $\alpha$ =2.5%, 1-$\beta$=80%).

**Participants included in the Intent To Treat analysis (ITT)**

The ITT analysis included all participants randomized to the primary objective and all severe cases randomized to the primary secondary objective. It compares the groups as they were randomized, in other words, all randomized patients are analysed in the group in which they were randomized and this analysis includes all patients included regardless of deviations from the protocols, i.e. regardless of the treatment they actually received and regardless of their progress or compliance during the study.
In rare cases, some subjects included in the study may be excluded from the analysis. This exclusion then applies to all statistical analyses included in the statistical analysis plan.
The decision to exclude a subject from the analysis is taken by the Scientific Council after documentation of the observation by the Methodology and Management Centre, without the knowledge of the treatment group and the subject's evolution after inclusion. The reasons that may lead to the exclusion of a subject from the analysis are:
- Subject not presenting the disease of interest
- Subject who has not signed consent or has withdrawn consent and opposes the use of his or her data
- Subject not meeting a major eligibility criterion including regulatory criteria
- Subject who has never taken the trial treatment (provided he or she was not aware of the group from which he or she was drawn).

**Participants included in Per Protocol analysis**

Per-protocol [PP] analysis includes only participants who received the complete randomized treatment strategy. It includes participants who complete the strategy for which they were randomly selected. In the OptiMA trial, follow-up is considered complete when the participant meets the following treatment adherence and follow-up requirements:
- Follow-up in UNTA is considered complete when treatment with RUTF has been prescribed a minimum of four times at the equivalent dose according to the allocated arm dosing table.
- Treatment is considered complete when 90% of the total prescribed dose of RUTF (by number of sachets) is within the dosage table of the allocated arm, rounded up to the next sachet.
- Follow-up in the village is considered complete when the time between each village follow-up visit is no more than 6 weeks.
Will be excluded from the PP analysis:
- Participants already excluded from the ITT analysis
- Participants who were randomized into the wrong stratum and therefore did not receive the treatment they should have received if they had been randomized into the correct stratum.
- Participants who permanently discontinued RUTF treatment from the trial for which they were drawn (excluding death).
Patients excluded from PP analysis should be excluded from the denominator.
For both RUTF and PP analysis, all data collected between inclusion and the end of the trial will be used. In other words, follow-up will be censored at the end of the trial for participants who were followed through to the end, or at the time of death for participants who died before the end of follow-up, or at the time of last contact for participants who were lost to follow-up before the end of follow-up.

## 2.2 SECONDAIRY ANALYSIS

### General principle

The occurrence of secondary endpoints will be compared between the two-randomization strategies when appropriate.

### Decision rule for superiority comparisons

For superiority comparisons of secondary outcomes, the usual comparisons will be made between the two arms, using the appropriate tests: Chi-2 for qualitative variables (comparison of proportions), Student or Kruskal-Wallis for quantitative variables (comparison of means or distribution of the variable), log-rank test for durations of occurrence of an event. If the p-value of the test is <0.05 then one arm will be considered superior to the other for the criterion in question.

## 2.3 STATISTICAL METHODS

Graphical representations will be associated with the analyses if relevant. The number and proportion of available data will be described for each variable. Statistical tests will be carried out bilaterally with a 5% alpha risk, unless specifically mentioned in the analysis plan.

Qualitative variables will be described in terms of numbers, percentages, and possibly accompanied by estimates of confidence intervals where relevant. If necessary, comparisons of qualitative variables will be made using tests of $\chi 2$, or $\chi$ 2 corrected, or exact Fisher, depending on the values of the headcount expected under the independence assumption.

Quantitative variables are described in terms of headcount, mean, standard deviation and confidence interval of the mean, median, range and interquartile range. If necessary, comparisons of quantitative variables will be made using the Student test (comparison of means) or the Wilcoxon test (comparison of distributions) or the Kruskal-Wallis test, depending on the distribution of the variable of interest.

Variables of the time to occurrence of an event will be described in terms of the incidence of occurrence, and the probability of occurrence over time, estimated by the Kaplan-Meier method. The incidence and probability of occurrence of events will be systematically accompanied by confidence interval estimates. If necessary, probability comparisons will be made by log-rank tests, or by proportional risk models, after verification of the assumption of proportionality of risks.

The date of origin is the inclusion date (V0) and the time of occurrence is the difference between the event date and the V0 date. The date of censorship will be:

- The date of the last follow-up carried out 6 months after randomization or
- The first of the following events after randomization: the first event of interest (the cured status for the primary secondary endpoint), death, or the last follow-up visit in the trial, for those who did not come at 6 months after randomization and never saw again afterwards.

## 2.4 CALCULATION CONVENTIONS FOR STATISTICAL ANALYSIS

### Calculation of time limits

- Delay between 2 dates **in days** = (Date 2 – Date 1)
- Delay between 2 dates **in weeks** = $\frac{(\text{Date 2} - \text{Date 1})}{7}$

- Delay between 2 dates **in months** = $\frac{(\text{Date 2}-\text{Date 1})}{30.4375}$
- Delay between 2 dates **in years** = $\frac{(\text{Date 2}-\text{Date 1})}{365.25}$
- Delay 6 months (M6) post-randomisation = $\frac{(\text{Date last followed}-\text{Date Randomization})}{30.4375} \geq$ à 6.
- Partially missing dates :

- If only the day is missing, the 01 of the month is imputed for the dates of birth, otherwise the 15 of the month for the other types of dates;
- If both the day and the month are missing, the 1st of July is imputed.

**Calculation of anthropometric indices'**

In this study, the table used for categorisation of the WHZ is the unisex table of DRC PECIMA guideline. This table corresponds to the boys WHZ WHO standard table. The anthropometric indices (WHZ, HAZ, WAZ) will also be calculated according to the WHO 2006 growth standards thanks to the package containing WHO tables for the software R® and recommended by WHO and UNICEF.

**Missing data**

The number of missing data is reported for each variable. The reasons for missing data will be documented as much as possible in order to interpret the results

**Missing data value**

The following values are used in the database to justify missing data:
- ND: Not done
- NA: Not applicable

### 2.5 SOFTWARE

Analyses will be performed with R® software (version 3.6.1 or higher).

## 3 ANALYSIS PLAN

All analyses will be presented by randomization arm. Some analyses will be stratified by category of MUAC at inclusion or categories of WHZ and/or HAZ at inclusion.

**PROTOCOL DEVIATIONS REPORTED**

Major deviations from the protocol reported by the national project leader or monitor will be listed.

### 3.1 DESCRIPTION OF INCLUSIONS

The number of patients included and randomized, included and non-randomized, followed at each visit, and having completed the study will be presented. Reasons for non-eligibility, as well as reasons for early study termination will be provided. Inclusions and follow-up in the study will be described according to the flowchart defined by the CONSORT recommendations.

**Compliance with eligibility and randomization criteria**

Inclusion criteria: the statistician checks that the answer to the criterion is 'yes'.

- Child aged between 6 and 59 months
- Meets one or more of the study's criteria for defining acute malnutrition: MUAC < 125 mm or WHZ ratio <-3 or Nutritional Oedema +, ++.
- Positive appetite test
- Resides in a health area included in the trial
- Signed Consent: verification that there is an extended consent signature date prior to or equal to the day of inclusion

Non-inclusion criteria: the statistician checks that the answer to the criterion is "no".

- Child with medical complications requiring referral to hospital
- Child already being treated for malnutrition
- Child with a known allergy to milk or peanuts
- Child with a known chronic pathology such as sickle cell disease, trisomy 21, congenital heart disease, neurological impairment.
- Child with oedema +++

**Compliance with randomization criteria:** the statistician checks that the answer to the criterion is "no".

- Child with a MUAC >= 125 mm and a WHZ <-3 and no oedema.
- Child with a sibling already included in the trial

**Flow diagram**

- Subjects screened for acute malnutrition (n) (source data aggregated from screening register)
- Subjects referred for an inclusion visit (n, %) (Aggregate source data from screening registry)
- Subjects who made an inclusion visit (n, %)
- Topics included in total (n, %)
- Subjects included randomized total and no arm (n, %)
- Non-randomized included subjects and reasons for non-randomization (n, %)
- Subjects who started the trial strategy (n, %)
- Subjects stopping strategy and reasons (abandonment, withdrawal of consent, lost to follow-up, transfer, relocation) (n, %)
- Subjects excluded from the intention-to-treat analysis (n, %)
- Reasons for Excluding Subjects from Intent to Treat Analysis (n, %)
- Subjects excluded from per-protocol analysis (n, %)
- Reasons for excluding subjects from per protocol analysis (n, %)

**Follow-up description**

- Subjects with complete follow-up (as defined in Chapter 2.1) by strategy (n, %)
- Subjects with incomplete follow-up (as defined in Chapter 2.1) by strategy (n, %)
- Cumulative follow-up in patient-weeks (sum of the duration of participation for each patient included: difference in number of weeks between the date of inclusion and the date of last contact in the study)

**Description of premature end of study**

- Status of patients at the end of the study (n)
- Reasons for premature termination of the test (n, %)

- Delay between inclusion visit and last news date

**End of treatment description**

- Subjects who stopped or changed trial strategy (n, %)
- Reasons for stopping the strategy (n, %)
- Delay between the randomization date and the strategy termination date
- Delay between inclusion date and strategy termination date

### 3.2 INCLUSION CHARACTERISTICS

**Socio-demographic characteristics**

- Age (months) in quantitative terms: delay between month and year of birth and date of randomization
- Age (months) in class: [6-24[; [24-59] months
- Sex
- Accompanying the child: mother, father, other
- Living mother (yes/no), if living mother, age (year)
- Father alive (yes/no)
- Literacy of the legal representative (yes/no), if yes: school level (primary, middle school, high school, higher education)
- Number of deliveries by the mother in quantitative terms
- Number of living siblings (same mother) in quantitative terms

If siblings and twin brother or sister, is he/she alive? (Yes/No)

If siblings, position of the child in the family birth order in quantity

If siblings, position of the child in the family birth order in class: 1-2, 3-5, >5

- Distance (in kilometres) from the village to the health centre in classes: < 5 km; [5-10];]10-15] ;>15

**Nutritional and anthropometric characteristics**

- Mid-Upper Arm Circumference (in mm)
- Mid-Upper Arm Circumference (in mm) in class: <115 mm; [115-119] mm; >= 120 mm
- WHZ
- WHZ in class: <-3; > -3 and <-2; > -2 and < -1.5; > -1.5
- HAZ
- HAZ in class: <-3; > -3 and <-2; > -2 and < -1.5; > -1.5
- WAZ
- WAZ in class: <-3; > -3 and <-2; > -2 and < -1.5; > -1.5
- Nutritional oedema in class: grade 1, grade 2, no oedema
- Degree of acute malnutrition in the classroom: severe/non-severe

If severe, routine antibiotic treatment (Amoxicillin) received (yes/no)

- Prescribed nutritional treatment (yes/no)
- Breastfeeding in progress (yes/no)

**Clinical characteristics**

- Rapid malaria screening test performed (yes/no) and if performed, result (positive or negative);
- Temperature (degrees Celsius);
- Temperature (degrees Celsius) in class: <37.5; >=37.5;

- Health problems observed (yes/no): non-bloody diarrhoea; anaemia and if clinical anaemia: haemoglobin value (g/dl) in quantitative; respiratory infection; vomiting; dehydration; intestinal parasitosis; dermatosis/skin infection; other health problems;
- Medical treatment received (yes/no): antimalarial drugs; antibiotic (other than routine treatment); oral rehydration salts; antiparasitic; iron/folic acid; intestinal parasitosis; other treatment;
- Source of classroom immunization data (notebook, declaration, immunization register);
- Immunization coverage at inclusion and at the end of the study (yes /no/ don't know)

### 3.3 MAIN OUTCOME ANALYSIS

**Success proportion calculation: PP and ITT**

V0 = randomization date; M6 = 6 months post-randomization.

- PP success proportion calculation : OptiMA arm and Standard arm at M6:

$$\frac{\begin{array}{c}Number\ of\ \ randomized\ children: alive\ with\ WHZ \geq -3\ AND\ MUAC \geq 125\ mm\ AND\ no\ oedema,\\ with\ no\ new\ episode\ of\ malnutrition\ other\ than\ V0\ AND\ \ with\ complete\ follow-up\\ (severe\ and\ no\ severe\ cases)\end{array}}{Number\ of\ randomized\ children\ included\ in\ PP\ analysis}$$

- ITT success proportion calculation : OptiMA arm and Standard arm at M6:

$$\frac{\begin{array}{c}Number\ of\ \ randomized\ children: alive\ with\ WHZ \geq -3\ AND\ MUAC \geq 125\ mm\ AND\ no\ oedema,\\ with\ no\ new\ episode\ of\ malnutrition\ other\ than\ V0\ AND\ \ with\ complete\ follow-up\\ (severe\ and\ no\ severe\ cases)\end{array}}{Number\ of\ randomized\ children}$$

### 3.4 MAIN SECONDARY OUTCOME ANALYSIS

**Recovery proportion calculation: PP and ITT**

- PP recovery proportion calculation :

$$\frac{\begin{array}{c}Number\ of\ randomized\ and\ recovered\ SAM\\ AND\ with\ complete\ follow-up\ in\ UNTA\end{array}}{Number\ of\ randomized\ severe\ cases\ \ included\ in\ PP\ analysis}$$

- ITT recovery proportion calculation :

$$\frac{Number\ of\ randomized\ and\ recovered\ SAM}{Number\ of\ randomized\ severe\ cases}$$

### 3.5 SECONDARY OUTCOME ANALYSIS

**Average consumption and cost of RUTF**

The average consumption of RUTF will be compared between the two strategies among recovered children included with SAM, in order to have two comparable groups. This analysis will only concern the episode of severe acute malnutrition at inclusion.

- Average RUTF consumption calculation in recovered SAM participants in each arm:

$$\frac{Number\ of\ RUTF\ sachets\ received\ by\ recovered\ SAM}{Number\ of\ recovered\ SAM}$$

The average consumption of RUTF will be compared between the two strategies among children in success regardless of the degree of acute malnutrition at inclusion in order to have two very comparable groups.

- Average RUTF consumption calculation in participants in success in each arm:

$$\frac{Number\ of\ RUTF\ sachets\ received\ by\ participants\ in\ success}{Number\ of\ particiants\ in\ success}$$

From the average consumption, we will calculate the average cost of RUTF treatment per child cured and per child successfully treated in each strategy. We will use as a reference the price of a sachet of RUTF according to the UNICEF pricing scheme in the country at the time of analysis.

**Average number of children cured for an equivalent amount of RUTF**

From the estimates of average RUTF consumption per SAM child at inclusion cured and per successful child in each strategy, we will calculate the average number of SAM children cured and the average number of successful children for a given amount of RUTF in each strategy.

- Calculation of the average number of recovered SAM with 100 cartons of RUTF, (one carton contains 150 sachets of RUTF):

$$\frac{15000\ sachets\ of\ RUTF}{Average\ number\ of\ consumed\ sachets\ by\ recoverd\ SAM}$$

- Calculation of the average number of participants in success with 100 cartons of RUTF (1 carton contains 150 sachets of RUTF):

$$\frac{15000\ sachets\ of\ RUTF}{Average\ number\ of\ consumed\ sachets\ by\ participants\ in\ success}$$

**Relapse to a new episode of acute malnutrition**

The relapse rate to a new episode of acute malnutrition will be compared between the two strategies among children with SAM according to the WHO definition (MUAC<115mm or WHZ <-3 SD or oedema) at inclusion and cured after RUTF supplementation. This analysis will concern the relapse to a new episode of SAM according to the WHO definition and to a new episode of acute malnutrition according to the trial

inclusion criteria (MUAC<125mm or WHZ<-3 SD or oedema). These analyses will be performed at 3 months post-recovery and 6 months post-inclusion. These analyses can be stratified by MUAC, WHZ, HAZ and WAZ categories.

- Calculation of relapse proportion to a new SAM episode (OMS definition) among SAM participants:

$$\frac{\text{Number of SAM at inclusion, recovered AND with a new episode of SAM (i.e. MUAC} < 115 \text{ OR WHZ} < -3 \text{ SD OR oedema)}}{\textit{Number of randomized SAM who recovered after RUTF treatment}}$$

- Calculation of relapse proportion to a new AM episode (inclusion criteria) among SAM participants:

$$\frac{\text{Number of SAM at inclusion, recovered AND with a new episode of AM (i.e MUAC} < 125 \text{ OR WHZ} < -3 \text{ SD OR oedema)}}{\textit{Number of randomized SAM who recovered after RUTF treatment}}$$

The rate of relapse to a new episode of acute malnutrition can be described for all children in the OptiMA arm cured after treatment with RUTF regardless of the degree of malnutrition at inclusion. This descriptive analysis could be stratified by category of MUAC, WHZ, HAZ and WAZ.

- Calculation of relapse proportion to a new AM episode (inclusion criteria) in OptiMA arm :

$$\frac{\text{Number of OptiMA participants at inclusion who recovered AND with a new episode of MA (i.e MUAC} < 125 \text{ OR WHZ} < -3 \text{ SD OR oedema)}}{\text{Number of recovered participants in OptiMA arm}}$$

**Standards Indicators of nutritional program**

In the OptiMA arm, this will involve comparing performance indicators for all children (severe and non-severe cases) to SPHERE standards. Only the episode of malnutrition presented for inclusion will be considered.

- **Recovery rate** :

$$\frac{\textit{Number of OptiMA participants who recovered}}{\textit{Number of OptiMA participants}}$$

- **Mortality rate**:

$$\frac{\textit{Number of OptiMA participants who died}}{\textit{Number of OptiMA participants}}$$

- **Defaulted rate** (a child is considered to have dropped out of UNTA follow-up at the 3rd absence of UNTA follow-up):

$$\frac{\textit{Number of OptiMA participants who defaulted}}{\textit{Number of OptiMA participants}}$$

The reference SPHERE indicators are: cure rate 75%, mortality rate < 5% and defaulted rate < 15%. The results of the OptiMA strategy will be described with their 95% IC, and will be considered to be consistent with SPHERE international standards if the lower limit of the 95% CI is greater than or equal to 75 for the cure rate and the upper limit of the 95% confidence interval is less than or equal to 5 for the mortality rate and 15 for the defaulted rate.

The following indicators will be described for all children who followed the OptiMA strategy and compared with results available in the literature:

- **Average length of stay of children who recovered**:

$$\frac{Sum\ of\ individual\ follow-up\ times\ (in\ days) of\ \ OPtiMA\ recovered\ participants}{Number\ of\ recovered\ OptiMA\ participants}$$

- **Average weight gain in** gr/kg/day:

$$\frac{Sum\ of\ individual\ weight\ gain\ of\ OptiMA\ participant\ (gr\ per\ kg\ per\ day)}{Number\ of\ recovered\ OptiMA\ participants}$$

In order to calculate the average weight gain, it is necessary to calculate beforehand for each child the individual weight gain of children recovered from UNTA in gr / kg / day : $\frac{W2-W1}{W} / T$

- W1 = Weight in kg on the day of inclusion or on the day of total oedema melting
- W2 = Weight in grams at last follow-up visit in UNTA
- T = Total number of follow-up days in UNTA (periods of hospitalization are not counted)

**Comparison of SPHERE indicators between the two arms:**

The comparison of SPHERE performance indicators between the two arms will be carried out only for participants with severe acute malnutrition at inclusion and will include the following indicators calculated for each arm:

- **Recovery rate** :

$$\frac{Number\ of\ SAM\ participants\ who\ recovered}{Number\ of\ SAM\ participants}$$

- **Mortality rate**:

$$\frac{Number\ of\ SAM\ participants\ who\ died}{Number\ of\ SAM\ participants}$$

- **Defaulted rate**:

$$\frac{Number\ of\ SAM\ participants\ who\ defaulted}{Number\ of\ SAM\ participants}$$

- **Average length of stay of children who recovered**:

$$\frac{Sum\ of\ individual\ follow-up\ times\ (in\ days) of\ SAM\ recovered\ participants}{Number\ of\ SAM\ recovered\ \ participants}$$

- **Average weight gain in** gr/kg/day:

$$\frac{Sum\ of\ individual\ weight\ gain\ of\ SAM\ recovered\ participant\ (gr\ per\ kg\ per\ day)}{Number\ of\ SAM\ recovered\ participants}$$

The method of calculating the average weight gain is similar to that mentioned above.

- **Average MUAC gain** in mm **:**

$$\frac{Sum\ of\ individual\ MUAC\ in\ mm\ between\ V0\ and\ the\ recovery\ visit\ of\ SAM\ participants}{Number\ of\ SAM\ recovered\ participants}$$

**Anthropometric evolution of children not eligible for RUTF at inclusion**

Children not eligible for RUTF at inclusion (non-severe cases of the Standard arm) will be described in terms of median anthropometric indices (MUAC, WHZ, HAZ, WAZ), % oedema at inclusion and during follow-up.

**Recovery and success among children with acute malnutrition associated with stunting at inclusion**

The success rate and cure rate of children who present at inclusion with HAZ <-2 and MUAC <125 mm or HAZ <-2 and WHZ <-3 will be described and compared to children who present at inclusion with HAZ >-2 and MUAC < 125 mm or HAZ >-2 and WHZ >-3 respectively.

**Anthropometric and Clinical Characteristics of Hospitalized Children**

The management of children hospitalized during follow-up in the study will be described and compared, if relevant, by arm in terms of anthropometric indices (MUAC, WHZ) at admission and discharge; reasons for admission and diagnosis at discharge; type of examination performed, type of treatment received, type of nutritional treatment received; average length of stay in hospital.

**Qualitative and Ancillary Study Analyses**

Secondary objectives related to qualitative data are not addressed in this document:

- Opportunities and barriers to the use of RUTF by children;

- Providers' perceptions of the implementation and monitoring of the two strategies.

Similarly, the analyses conducted in the framework of possible ancillary studies are not the subject of this document.