Conflict of Interest

The author has declared no conflict of interest.

Plateforme CORAL – ALIMA / Inserm

Clinical & Operational Research Alliance

Optimising malnutrition treatment in children aged 6-59 months: Primary outcome of a randomised control trial in Democratic Republic of Congo

OptiMA-DRC

May 19th, 2021 – London

Cécile CAZES

Registered at ClinicalTrials.gov, number NCT03751475.
Ethical approval with annual renewal from the DRC National Ethics Committee (CNES approval # 94/CNES/BN/PMMF/2018) and from the Ethics Evaluation Committee of the French National Institute for Health and Medical Research (Inserm approval # 18-545).

Introduction

- **47 million children <5** affected by acute malnutrition (AM) of whom **14 million were severe cases** *(Joint Child Malnutrition Estimates 2020 edition)*

- Underlying cause of **875 000 deaths worldwide** *(Black, Lancet, 2013)*

Treatment coverage <20%

- Two separate malnutrition treatment program, moderate acute malnutrition (MAM) and severe acute malnutrition (SAM), both globally underfunded

- Classification unnecessarily complex

- Dosage treatment not optimal and paradoxical

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	Standard DRC Protocol		OptiMA Protocol
	Severe cases (SAM)	**Moderate cases (MAM)**	
Case definition	MUAC<115mm or WHZ<-3 or Bipedal oedema	MUAC [115mm- 124] or -3 < WHZ <-2	MUAC < 125mm or Bipedal oedema
Product and dosage strategy	RUTF According to the weight	RUSF At a fixed dosage	RUTF According to MUAC status and weight <115 or Edema / [115-119] / [120-124]
Dosage in Kcal/kg/d	150-200	1sachet /d (=500 Kcl/d)	170-200 / 125-190 / 50-160
Discharge criteria	MUAC≥125mm **or** WHZ ≥-1.5 Z score **and** no oedema for two consecutive weeks	MUAC ≥125 mm **or** WHZ ≥−1.5 no oedema for two consecutive weeks If after recovery from SAM: MUAC≥125 mm **and** WHZ ≥−1.5 **and** discharge after 3 months	MUAC≥125mm **and** no oedema for two consecutive weeks **and** minimum 4 weeks in program **and** good clinical health

MUAC=mid-upper-arm circumference.
WHZ= weight for-height z-score
RUTF=ready to use therapeutic food.
RUSF=ready to use supplementary food.

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

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OptiMA scope

Better allocating available resources by:

- Treating all children with MUAC<125 or oedema
- With one product at a gradually reduced dose as child's weight and mid upper arm circumference (MUAC) increase

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Primary objective

Determine, 6 months after inclusion, whether the OptiMA strategy led to a rate of favourable outcome that is non-inferior to the standard DRC protocol in use at the same outpatient health facilities among uncomplicated children aged 6-59 months with a MUAC <125 or a WHZ<-3 or nutritional oedema

Methodology

- Design: Non-inferiority individually randomized unblinded clinical trial
- Setting: 4 health centres, 60 villages, 1 district hospital in Kamuesha district of Kasai province
- Population: 6-59 months and MUAC <125 mm OR WHZ<-3 OR nutritional oedema (+,++) without medical complications, informed consent
- Enrolment strategy : monthly active screening in the 60 villages and passive screening during outpatient visits in the 4 health centre included
- Follow-up trial: **weekly outpatient visits** at health centre for children with RUTF supplementation and **bimonthly home visits** for children without RUTF supplementation **until 6 months post-inclusion**

Trial conducted from July 2019 to July 2020

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SCIENTIFIC DAYS

Outcomes

Primary outcome	**890 participants**
Favourable outcome at 6 months post-inclusion	- Alive **and** - Not acutely malnourished per the definition applied at inclusion **and** - No additional episode of acute malnutrition throughout the 6- month observation period
Main analysis	- **Non-inferiority analysis** comparing both arms on an **intention-to-treat (ITT) and per-protocol (PP)** basis *-> **demonstrated if the upper-bound of the 95%CI of the difference** between Standard-OptiMA arms is **<10%** (one-sided test, α =2·5%, 1-β=80%)* - **Superiority** considered and secondary analyses performed **if** non-inferiority demonstrated *-> **demonstrated if** the upper-bound of the 95%CI of the difference between Standard-OptiMA arms is **<0%** (one-sided test, α =2·5%, 1-β=80%)*
Secondary outcomes	- Anthropometric changes - RUTF/RUSF consumption, length of treatment - Nutrition status improvement : MUAC >124 without oedema (2 consecutives visits)

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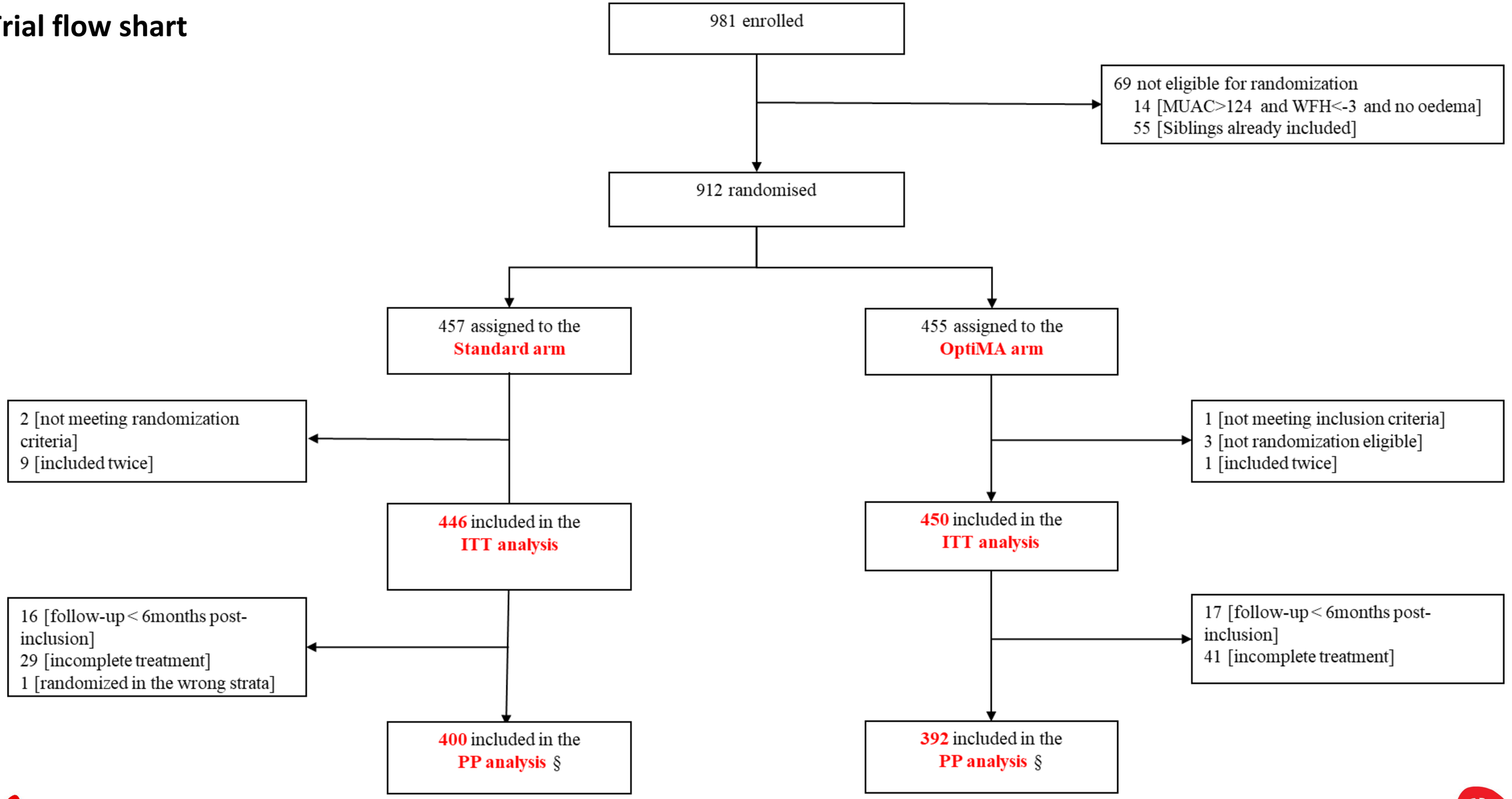
Trial flow shart



§Per Protocol:
- minimum 4 weekly rations RUTF prescribed in accordance with the dosage table of the respective randomization arm and
- RUTF ration received was minimum 90% of the correct number in accordance with the dosage table of the respective randomization arm and
- maximum interval between two visits was 6 weeks.

Baseline characteristics, ITT SET (N=896)

	Standard N=446	OptiMA N=450
Girl	221 (50%)	229 (51%)
Age (months)	17 (11-29)	16 (9-27)
Age 6-24 (months)	278 (62%)	290 (64%)
Health center's distance from village >14 km	44 (10%)	53 (12%)
MUAC (mm)	120 (114-123)	120 (114-122)
MUAC <115 mm	119 (27%)	123 (27%)
Nutritional oedema	43 (10%)	35 (8%)
WHZ <-3§	95 (24%)	99 (24%)
HAZ <-3	202 (45%)	182 (40%)
WAZ <-3§	209 (52%)	199 (48%)
Malaria confirmed and treated	216 (48%)	208 (46%)
Diarrhea declared	16 (4%)	16 (4%)
Severe cases (MUAC<115 or WHZ<-3 or oedema)	200 (45%)	198 (44%)
RUTF begun	**200 (100%)**	**198 (100%)**
Amoxicillin received	200 (100%)	198 (100%)
Moderate cases (MUAC 115-124 and WHZ≥-3)	246 (65%)	252 (66%)
RUTF begun	0 (0%)	**252 (100%)**
RUSF begun	**65 (26%)**	0 (0%)

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MUAC= mid-upper-arm circumference. WHZ= weight for-height z-score. WAZ= weight-for-age z-score. HAZ= height-for-age z-score
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Follow-up characteristics, ITT SET (N=896)

	Standard N=446	Optima N=450
Completeness of follow-up		
Completed 6 month follow-up	429 (96·2%)	432 (96·0%)
Family moved out of study area	16 (3·5%)	17 (3·8%)
Death	1 (0·2%)	1 (0·2%)
Hospitalized at least once	32 (7·2%)	43 (9·5%)
Albendazole	436 (98%)	436 (97%)
Vitamin A	441 (99%)	446 (99%)
Caretaker trained to MUAC use	437 (98%)	445 (99%)
Number of follow-up visits per child*	14 (12-15)	14 (13-16)

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SCIENTIFIC DAYS

Primary outcome

	Standard	OptiMA	Difference (95% CI)
Intention-to-treat population	**N=446**	**N=450**	
Favorable outcome	**282 (63·2%)**	**325 (72·2%)**	**-9·0% (-15·9% to -2·0%)**
New episode(s) of AM within 6 months, resolved	98 (22·0%)	96 (21·3%)	
New episode(s) of AM and unresolved at 6 months	**37 (8·3%)**	4 (0·9%)	
Initial episode of AM unresolved at 6 months	12 (2·7%)	7 (1·6%)	
Discontinued trial	16 (3·6%)	17 (3·8%)	
Death occurred during the 6 months follow-up	1 (0·2%)	1 (0·2%)	
Per protocol population	**N=400**	**N=392**	
Favorable outcome	**260 (65·0%)**	**291 (74·2%)**	**-9·2% (-16·4% to -1·9%)**
New episode(s) of AM within 6 months, resolved	93 (23·2%)	93 (23·5%)	
New episode(s) of AM and unresolved at 6 months	34 (8·5%)	3 (0·8%)	
Initial episode AM unresolved at 6 months	12 (3·0%)	5 (1·3%)	
Death during the 6 months follow-up	1 (0·7%)	1 (1·0%)	

AM= acute malnutrition

Non-inferiority shown on the ITT and PP set (*upper bound of 95% CI of favourable outcome difference is < 10%)*

Superiority shown on the ITT and PP set *(upper bound of 95% CI of favourable outcome difference is < 0%)*

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Secondary outcomes, ITT set (N=896)

	Standard N=446	OptiMA N=450	p-value
Anthropometric improvement			
MUAC <125 mm at last visit	54 (12%)	18 (4%)	<0·0001
Weight gain (g), *median (IQR)*	1600 (IQR 1000- 2200)	1700 (IQR 1200-2400)	0·0035
MUAC gain (mm), *median (IQR)*	12 (IQR 8-16)	13 (IQR 9-18)	0·0162
Children with MUAC>124 and no oedema during two visits ≤ 12 weeks of follow-up	284 (64%)	386 (86%)	<0·0001
Nutritional support received during entire trial			
Children receiving RUTF or RUSF or both	315 (71%)	450 (100%)	<0·0001
RUTF/RUSF distributed (sachets), *median (IQR)*	133 (IQR 65-184)	64 (IQR 47-98)	<0·0001
RUTF/RUSF duration (days), *median (IQR)*	49 (IQR 35-70)	42 (IQR 35-70)	0·2737

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Nutritional products costs	**Standard N=446**	**OptiMA N=450**
TOTAL RUTF/RUSF distributed	315 boxes (287 RUTF+18 RUSF)	247 boxes (RUTF)
TOTAL RUTF/RUSF costs	**$12 753 USD**	**$10 374 USD**

Around 30% more children with nutritional support and 20% nutritional products distributed less in the OptiMA arm

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Secondary results in children with MUAC<115 or oedema at inclusion

	MUAC<115 mm OR oedema		
	Standard N=158	**OptiMA N=154**	**p value**
Anthropometric improvement			
Children with MUAC>124 and no oedema (2 visits) ≤ 12 weeks of follow-up	120 (76%)	117 (76%)	0·9792
Weight gain until the end of trial follow-up, (g)	1600 (1100- 2400)	1900 (1200-2600)	0·0550
MUAC<125mm at last visit in the trial	33 (21%)	10 (7%)	0·0004
Favourable outcome at 6 month	94 (59%)	108 (70%)	0·0020
New episode(s) of AM within 6 m, resolved	27 (17%)	28 (18%)	
New episode(s) of AM and unresolved at 6 m	21 (13%)	2 (1%)	
Initial episode AM unresolved at 6 m	8 (5%)	4 (3%)	
Discontinued trial	8 (6%)	12 (8%)	
Nutritional support received during entire trial			
Children receiving RUTF during trial	158 (100%)	154 (100%)	1·0000
RUTF distributed (sachet)	147 (119-194)	85 (69-145)	<0·0001
RUTF length of treatment (days)	49 (42-77)	56 (42-89)	0.6730
Children receiving RUSF treatment	0	-	

Data are median (IQR) - n (%) –
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Main limitation

- Not a multi-center trial

Strengths

- Individual randomized design with a 6 month follow-up period after inclusion
- Follow-up in village beyond health centre
- Common resources limited settings context where the two separated standard nutrition program are not fully functional
- Accumulating body of evidence: safe, feasible and advantageous to treat children with MUAC <125mm with a single nutritional product at a gradually reduced dose

Interpretation

- The **OptiMA** malnutrition treatment protocol **was superior** to the current DRC national

- **30% children treated more by using 20% less RUTF and RUSF**, with significantly **better weight and MUAC gain over 6 months.**

- Progressive RUTF dose reduction showed **no evidence of harm in children with MUAC < 115** mm.

- These findings could have **substantial individual and public health implications**

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Acknowledgments

Cazes©

We are indebted to the caretakers and children who participated in the study, the personnel of the DRC Ministry of Health, the community health workers, the ALIMA operational team on the ground.

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