Design and pre-testing of lipid-based, ready-to-use foods for the prevention and treatment of malnutrition in low-resource settings

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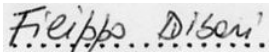
Source: Filippo Dibari, Benin 2006.

Declaration

I, Filippo Dibari, confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I confirm that this has been indicated.



(Filippo Dibari)

Abstract

Background

Managing child and adult undernutrition is a global public health priority. In poor settings, improved specialised products are needed for treatment and prevention, including for chronic disease/HIV.

Objective

To develop a method for the design and pre-clinical testing of novel, low-cost Ready-to-Use Therapeutic Foods (RUTF), to be also applied to supplementary/complementary feeding interventions.

A **method** was developed and tested, using four sequential studies, with HIV-positive Kenyan adults with severe acute malnutrition (case-study).

A **qualitative study** explored adherence and consumption barriers with the current UN-standard peanut/milk-powder-based therapeutic formulation (P-RUTF).

A **study using Linear Programming** (LP) designed an improved, cheaper formulation soy/maize/sorghum-based (SMS-RUTF), considered accurate if: its manufactured prototype, compared to calculated values; it had a measured energy density difference (EDD) <10%; a protein or lipid difference (P/LD) <5g/100g.

An **acceptability study** (4-weeks-cross-over design; washout one-week) compared use of SMS-RUTF against P-RUTF (n=41), using 18 consumption/safety/preference criteria.

Based on a **literature review** (28 randomized controlled trials of micronutrient supplementation; outcomes: increased survival and CD4 cell count, reduced viral load), four criteria to determine micronutrient specifications for the SMS-RUTF fortification were developed and applied.

Results

The reported compliance with the prescribed RUTF was relatively low, and informed the necessary formulation improvements.

The LP-determined formulation was accurate (EDD: 7%; PD and LD: 2.3 and 1.0g/100g).

The LP-based prototype was acceptable and safe, but with an average number of days of nausea and vomit (0.16 and 0.04 d) occurred with a higher frequency ($P < 0.05$) than in the control (0.09 and 0.02 d).

The existing evidence for determining micronutrient specifications for SMS-RUTF posed some challenges for the development of manufacturing specifications. Twelve of the micronutrient specifications developed for SMS-RUTF fortificant premix were equivalent to the UN minimum standards; eleven were 2 to 10 times higher.

Conclusions

The proposed set of methods can be used to design and pre-clinically test improved/cheaper RUTF products, targeting malnourished adults. Novel formulations should be clinically trialled before widespread-use.

Abbreviations and acronyms

Abbreviation	Complete form
ACF	Action Contre la Faim
AIDS	Acquired Immunological Deficiency Syndrome
ART	Anti-Retroviral Therapy
BMI	Body mass index
CI	Confidence Interval
CIAA	Confédération des Industries Agro-Alimentaires de l'UE - Confederation of the food and drink industries of the EU
CMAM	Community-based Management of Acute Malnutrition
COREQ	Consolidated criteria for reporting qualitative research
CSB	Corn Soy Blend
CTC	Community-based Therapeutic Care
DALY	Disability-adjusted life-years
DDS	Diet Diversity Score
DFE	Dietary Folate Equivalents
DFID	Department for International Development
DOTS	Directly Observed Treatment Services
DRI	Dietary Recommended Intakes
EAR	Estimated Average Requirement
EDD	Energy Density Difference
EFSA	European Food Security Agency
EPZ	Export Processing Zone
ERNA	European Responsible Nutrition Alliance
FANTA	Food and Nutrition Technical Assistance
FAO	Food and Agriculture Organization
FBF	Fortified blended food
FCD	Food Composition Database
FDA	Food and Drug Administration
GAIN	Global Alliance for Improved Nutrition
GAM	Global Acute Malnutrition
GDP	Gross Domestic Product
GNC	Global Nutrition Cluster
HAART	HAART - Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HTP	Harmonized Training Package
IFAD	International Fund for Agriculture
iLiNS	The International Lipid-Based Nutrient Supplements
ILSI	International Life Sciences Institute
IOM	Institute of Medicine
IQR	Interquartile Range
IRD	Institute for Research and Development
KEMRI	Kenya Medical Research Institute
LNS	Lipid-based Nutrient Supplement
LNS	Lipid nutrient supplement

Abbreviation	Complete form
LOAEL	Lowest-Observed-Adverse-Effect Level
LP	Linear Programming
MAM	Moderate Acute Malnutrition
MDG	Millennium Development Goal(s)
MoH	Ministry of Health
MSF	Médecins Sans Frontiers
MTCT	Mother to Child Transmission
MUAC	Middle Upper Arm Circumference
MUAC	Mid-Upper Arm Circumference
NGO	Non-Governmental Organization
NHMRC	National Health and Medical Research Council
NOAEL	No-Observed-Adverse-Effect Level
PDCAAS	Protein Digestibility-corrected Amino Acid Score
PEM	Protein Energy Malnutrition
PEPFAR	President's Emergency Plan for AIDS Relief
P-RUTF	Peanut butter, milk powder based RUTF
p-value	Value of statistical probability
QFD	Quality Functional Deployment Model
RCT	Randomized Controlled Trial
RDA	Recommended Dietary Allowances
RDI	Reference Daily Intake
RNI	Recommended Nutrient Intake
RUCF	Ready-to-Use Complementary Food
RUF	Ready-to-Use Food
RUSF	Ready-to-Use Supplementary Food
RUTF	Ready-to-Use Therapeutic Food
RUTFH	Ready-to-Use Therapeutic Food for HIV/TB
SAM	Severe Acute Malnutrition
SD	Standard Deviation
SFP	Supplementary Feeding Programme
SMS-RUTFh	Soy, maize, sorghum RUTF specific for HIV and TB
STD	Standard Deviation
TB	Tuberculosis
TFC/P	Therapeutic Feeding Centre/Programme
TFD	True Faecal Digestibility
TFP	Therapeutic Feeding Programme
UCL	University College London
UN	United Nations
UNHCR	United National High Commission for the Refugees
UNICEF	United Nations International Children's Fund
USD	United States Dollar
USDA	United States Department of Agriculture
WAM	Weight-for-age % of median
WAZ	Weight-for-age Z-score
WFDAS	World Food Dietary Assessment System
WFP	World Food Programme
WHM	Weight-for-height % of median

Abbreviation	Complete form
WHO	World Health Organization
WHZ	Weight-for-height Z-score
WPC	Whey Protein Concentrate
WPHNA	World Public Health Nutrition Association
WTO	World Trade Organization

Table of Contents

Table of Figures

Tables

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Paper co-authors: Andrew Seal (UCL), Paluku Bahwere (Valid International), Helena Huerga (MSF), Abel Hailu Irena (Valid International), Victor Owino (Valid Nutrition), El Hadji Diop (Valid International), Isabelle Le Gall (MSF), David Mwaniki (KEMRI). Some of them became friends too.

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Personal: last but not least at all, I also dedicate this thesis to my "life-partner-in-crime" Paolo Paron for believing and supporting the realization of my wildest dreams, to my parents for having transferred onto me their embarrassing stubbornness, to my two sisters Camilla Dibari e Matilde Strippini for existing and genuinely loving me.

Foreword

Almost 9 million child deaths every year,
one-third of the total, are related to undernutrition [1].
More than any other cause of mortality [1].

However, the problem of malnutrition remains a matter of shame [2].

Thesis outline

In **Chapter 1**, I present the background to this thesis, outlining how undernutrition is a current global public health issue. I also describe the evolution of the management of acute malnutrition, highlighting lipid-based, ready-to-use food (RUF) as a key intervention within the treatment package, and identify the current problems and knowledge gaps that urgently need to be solved and filled.

In **Chapter 2**, I present the aims, the objectives, the study plan and the research questions.

In **Chapter 3**, I describe and discuss a method to understand the factors affecting usage of current formulations of ready-to-use foods (sub-study 1). As a case study, I tested this method by investigating the adherence to a therapeutic nutrition intervention, in a Kenyan HIV/TB programme.

In **Chapter 4**, I describe and discuss a method to design cheaper RUF formulations, fulfilling macro-nutrient requirements and food-related standards (sub-study 2).

In **Chapter 5**, I describe and discuss a method to test the acceptability and the safety of a novel RUF formulation (sub-study 3). I tested this method comparing the consumption, the

safety and the preference of a cheaper RUF with the most commonly used product with HIV/TB patients in Kenya.

In **Chapter 6**, I propose and discuss an evidence-based method to derive RUF micronutrient specifications for malnourished groups, when requirements are not available (sub-study 4).

In **Chapter 7**, I collate the key findings from the four studies into a method framework to design RUF products, discussing the product design model, the generalisability of the framework to other formulations, its limitations and its implications for nutrition treatment programmes, concluding with recommendations for policy and research.

The **Appendices** contain other materials which are not included in the main body of the thesis for reasons of space and flow. Also listed are publications arising from and closely related to the research described.

Role and description of the PhD student

This thesis would not have been possible without the help and support of many individuals and organizations. Following the time sequence of the research work, their contribution is summarized in this section, and was agreed with both the sponsor of this study, the organization Valid International, and my PhD supervisors.

Before the enrolment into the PhD programme

My wish to fight hunger in poor countries started in my early adolescence, grew during my studies (MSc) in Food Science and Engineering (University of Udine, Italy; 1988-1993), which included a six month research project in Burundi, and consolidated during four years of community-based work with underprivileged communities in the Amazon forest of Brazil. However, providing more and better food to groups in need proved to be inadequate to my personal quest of working with hunger.

Those experiences induced me (i) to look closer at undernutrition, at ways of assessing the size of the problem at community level, at the effects of such problems, and (ii) to develop efficient interventions and solutions. Therefore, after a few years of work at FAO and in IFAD programmes, and missions in Mozambique, Somalia, and Salvador, I completed a MSc course in Public Health Nutrition, at the London School of Hygiene and Tropical Medicine (2002-2003).

In 2003-2004, after experience as programme manager in a therapeutic feeding programme (Democratic Republic of Congo), I engaged with nutrition research activities at the Institute of Child Health (UCL) and WFP under the supervision of Dr Andy Seal, my tutor in this thesis. In our assignment, we looked at the impact of WFP fortified blended food in preventing pellagra in Angola.

In 2005, I started to work with the organization Valid International, covering three areas of responsibility: the design and production set-up of novel ready-to-use therapeutic foods, the undertaking of programme coverage surveys, and the set-up of community-based programmes for the management of acute malnutrition in African countries (Benin, Niger,

and Kenya, among others), in Asia (Bangladesh, Sri Lanka and Vietnam) and in central America (Haiti).

During the enrolment into the PhD programme

Based on the work experience gained, in 2006, with the support from Valid International, and a fund available from Concern World Wide, I conceived the scope of this thesis. Its focus consists of the development of methods for the design and pre-testing of ready-to-use foods to prevent and manage acute malnutrition.

I officially enrolled into the UCL MPhil programme in November 2007 and Prof Tomkins accepted to become my second supervisor, providing important guidance on the latest drafts of my doctorate. In 2009, upgrading to the UCL PhD programme, the examining commission helped me in achieving what is the current doctorate structure. Since 2007, Dr Seal provided regular feedback on my research activities, and, based on the sub-study 1, 2 and 3 of this thesis, helped me in getting three papers published in peer-reviewed journals (see section **With first authorship** at page 327).

In collaboration with the NGO Médecins San Frontiers (MSF), in a Kenyan HIV clinic located on the Lake Victoria, I conducted the data collection of the first and the third core-studies, described here. The development of the linear programming based method for the second sub-study was supported by the collaboration with the largest food aid manufacturer in Africa. In Nairobi, Insta Limited factory produced, at both small and large scales, the ready-to-use food prototypes, while its laboratory conducted the chemical analysis.

The methodological approach and the results in the fourth and last sub-study, looking at RUF micronutrient specifications, when requirements are not available, was initially discussed with Professor Friis from the University of Copenhagen, and its later stages discussed with both Professor Mike Golden and MSF (Susan Sheperd and Saskia Van der Kam).

Follow up of the PhD programme

The topic of this thesis is consistent with my current commitments. Since November 2012, I

work as Chief of the Nutrition Unit in the Mozambique Country Office of the World Food Programme of the United Nations. With this current position, I manage an implementation research controlled trial, funded by the Children Investment Foundation Fund (CIFF; London), looking at prevention of stunting in children under two years of age (n=150,000 in 3.5 years will be enrolled in the intervention group only), and using lipid-based, ready-to-use complementary foods. The trial outcomes will shape future policies in stunting prevention. Furthermore, in collaboration with other international agencies, academic bodies and most of all the local Mozambican Government, I am looking into local/regional design, testing and production of improved lipid-based, ready-to-use foods for treatment of chronically ill (HIV/TB) Mozambican adults.

1 Background

1.1 Malnutrition: a global public issue

It is an exciting time to work and research in the area of malnutrition. In a recent policy paper, the WFP suggests that "recent years have seen rapidly growing interest in nutrition, galvanized by The Lancet medical journal's 2008 series, which describe the scale and consequences of maternal and child undernutrition, and identify proven interventions and strategies for reducing this burden"[3]. It is, therefore, not surprising that, in middle and low-income countries, "from 2004 and 2007, an estimated USD 350 million were committed to nutrition programming annually"[4], showing a slow but steady increasing trend in this area of interventions.

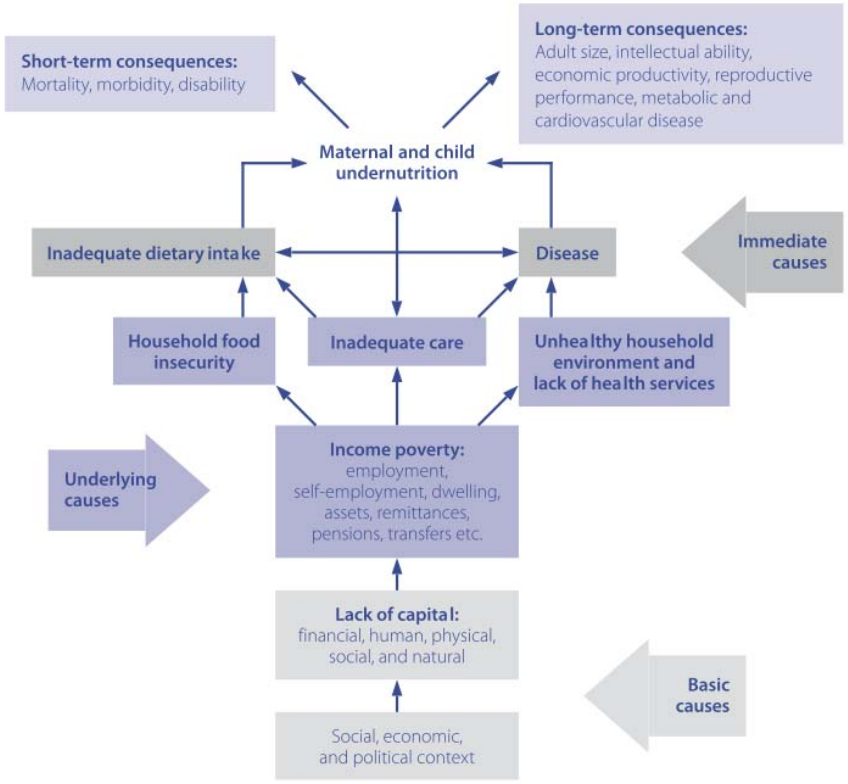
1.1.1 Malnutrition and its sub-forms

Malnutrition is a general term, which includes different forms of both undernutrition and overnutrition. In general, malnutrition is a physical condition "which makes individuals more susceptible to disease"[5] and sometimes death. The present research focuses on the forms of undernutrition occurring with high prevalence in "low-income and middle-income economies, sometimes referred to as developing economies" by the World Bank[6].

During the last decades, the classifications of malnutrition and its sub-forms evolved through a large number of definitions[7–9]. In this thesis, these are mostly based on the "Harmonized Training Package (HTP) - Resource Material for Training on Nutrition in Emergencies"[5], prepared by Nutrition Works on behalf of the UN Global Nutrition Cluster (GNC). The following sections summarize the definitions of under- and overnutrition.

The HTP defines undernutrition as “an insufficient intake of energy, protein or micronutrients that in turn leads to nutritional deficiency. Undernutrition encompasses

Figure 1 - Nutrition conceptual framework



Adapted by Levine and Chastre[479] *from UNICEF.*

stunting, wasting and micronutrient deficiencies”. When present, this form of malnutrition “weakens the immune system and increases the risk and severity of infections”[3]. Overnutrition is defined as “abnormal or excessive fat accumulation that may impair health”[10]. Undernutrition is common in low-income groups in developing countries and is strongly associated with poverty[5]. Many low- and middle-income countries are facing a "double burden" of both under and overnutrition[10]. In this thesis, overnutrition is not covered in depth. This is because this form of malnutrition is relatively less associated with emergency or low-resources countries, compared to high-resource world regions.

Undernutrition is “a complex, multi-faceted problem”[3] and the consequence of a large number of health and environmental factors (Figure 1). However, inadequate dietary intake

or low food absorption, in the presence of one or more diseases are the immediate causes. Morbidity is associated with loss of appetite, malabsorption and/or loss of nutrients through diarrhoea or vomiting[5]. “The ill persons need more nutrients to rehabilitate and if they do not meet their needs they become malnourished”[5]. This relationship is known as the malnutrition-infection cycle[11].

Table 1-Classification of malnutrition forms .

	Form of Malnutrition		Anthropometry (WFH, BMI) and/or Mortality Risk (MUAC)			
			Infant <6 months	Children 6-59 months	Children 5-19 years	Adult
Undernutrition	Acute (Wasting)	Severe	Clinical signs* and risk factors**	Weight-for-height Z-score: < -3 SD MUAC: <115mm MUAC for age Z-score: < -3 SD	BMI-for-age Z-score: <-3SD~	MUAC: 170mm (men) & 160 mm (women)+ BMI: <16 kg/m²
		Moderate	Clinical signs* and risk factors**	Weight-for-height Z-score: < -2 SD to ≥ -3 SD MUAC: ≥ 115mm & < 125mm	BMI-for-age Z-score: ≥-3SD & <-2SD~~	MUAC: <190 mm (women) & 200 mm (men) BMI: <17 to ≥16
		Nutritional oedema	-	Yes	Yes	Yes
	Chronic (Stunting)	Severe	-	Height-for-age Z-score: < -3 SD	-	-
		Moderate	-	Height-for-age Z-score: <-2 SD to ≥-3 SD	-	-
	Underweight	Severe	-	Weight-for-age Z-score: < -3 SD	-	-
		Moderate	-	Weight-for-age Z-score: <-2 SD to ≥-3 SD	-	-
Overnutrition	Overweight	-	-	BMI-for-age Z-score: >+1SD to ≤ +2SD	BMI-for-age Z-score: >+1SD to ≤ +2SD	BMI: ≥25 to <30 kg/m²
	Obesity	-	-	BMI-for-age Z-score: ≥+2SD	BMI-for-age Z-score: ≥+2SD	BMI: ≥30 kg/m²

Adjusted from HTP 2011[5], unless specified. HTP, Harmonised Training Package; MUAC, middle upper arm circumference; SD, standard deviation; BMI, body mass index.

* E.g. oedema, visible wasting, too weak to suckle, not gaining weight despite feeding.

** E.g. insufficient breast milk, absence of mother.

~ The reported classification reports “severe thinness” rather than SAM or wasting.

~~ The reported classification reports “Thinness” rather than MAM.

+ Source: Ferro-Luzzi (1996)[12].

In undernutrition, acute, chronic and underweight are often referred to as sub-forms. In Table 1, these are classified separately. However, malnourished people can also present two or three forms simultaneously[5], showing a higher morbidity risk[13]. The following sections describe them in more detail.

1.1.1.1 Acute malnutrition in children, adolescents and adults

Clinical forms of acute malnutrition can be defined by the characteristics of severe wasting, also called marasmus, and/or bilateral pitting oedema, found in Kwashiorkor as well as in a range of other clinical signs.

Marasmus is a form of severe undernutrition, referred to alternatively as non-oedematous malnutrition. The Wellcome Classification associated marasmus with "severe wasting of fat and muscle, which the body breaks down to make energy leaving 'skin and bones'. A child with marasmus is extremely thin with a wizened 'old man' appearance"[5] (see Figure 2).

Kwashiorkor is a form of severe undernutrition, also referred to as oedematous malnutrition. Kwashiorkor is associated with growth failure (when compared with healthy children) and characterised by oedema, loss of appetite, thin, sparse or discoloured hair and skin with discoloured patches that may crack and peel. Kwashiorkor is associated with a pitting oedema affecting both sides of the body (bilateral) (see Figure 2). Oedema is defined by the HTP as "swelling from excessive accumulation of watery fluid in cells, or tissues".

Box 1 – Use of Z-scores in nutritional indices

In the latest WHO classification, MUAC-for-age, Weight-for-height, Height-for-age, and Weight-for-age are indices based on the use of Z-scores.

The Z-score describes how far a measurement is from the median, or the average in a healthy population. In 2006, WHO released growth curves aiming to set an international standard of how children "should grow when free of disease, and when their care follows healthy practices such as breastfeeding and non-smoking"[480].

For example, the BMI-for-age Z-score, another index calculated for an individual, indicates how many standard deviation units an individual's BMI value is away from the median for the same age in the WHO standards[481]. The index can be positive or negative. If positive, the index suggests that the BMI is higher than the median value of an individual of the same age in the WHO reference. If negative, the BMI is lower than the same reference.

Ninety-five percent of the WHO Growth Standard population has anthropometric Z-scores between -2 and +2. This range is considered normal. For example, if a child's Z-score falls outside (>+2 or <-2), this signals a deviation from the norm in his or her nutritional status [5].

Marasmic kwashiorkor is a form of severe undernutrition diagnosed by the presence of

severe wasting and bilateral oedema.

Risk of short-term death is assessed by the circumference of the left middle upper arm (MUAC)[1415], whereas nutritional indices referring to Z-scores (explained in Box 1) are more indicated to define the anthropometry of children presenting moderate (MAM) or severe acute malnutrition (SAM). In addition, the presence of bilateral pitting oedema is considered diagnostic for SAM.

Different cut-offs values for those criteria are used for different age groups (Table 2). Acute malnutrition can be found in very young children. Infants under six months of age affected by SAM or MAM, presenting oedema, and/or visible wasting, are often too weak to suckle, and may not gain weight despite correct feeding practices. Anthropometric measurements cut-offs are currently not available.

Figure 2 – Clinical forms of severe acute malnutrition: marasmus and bilateral pitting oedema with skin changes of kwashiorkor.

Source: Valid International (2007).

In SAM, children with less than five years of age show a weight-for-height Z-score lower than -3 standard deviations (SD). Middle upper-arm circumference (MUAC) lower than 115 millimeters suggests high risk of short-term mortality.

Box 2 - Formula to calculate body mass index

Body mass index =

Weight (kg) / height^2 (m)

Children of the same age, affected by MAM, are identified by weight-for-height Z-score ratio equivalent to or higher than -3 SD, up to a maximum of -2 SD. MUAC should be equivalent to, or higher, than 115 mm, and lower than 125 mm to identify children at moderate risk of short-

term death.

In children and adolescents (5 to 19 years of age), SAM is defined respectively by a body mass index (BMI)-for-age Z-score lower than -3 SD, or, in case of MAM, by the same index equivalent to or higher than -3 SD and lower than -2 SD.

Severely wasted male and female adults often present a MUAC respectively of 170 and 160 mm according to Ferro-Luzzi and James[12], and/or a BMI lower than 16 kg/m^2. In the moderate acute form, the MUAC cut-off values for males and females are 200 and 190 mm. BMI is calculated based on the weight (in kg) divided by the square of the height (in m) of the individual (see Box 2).

However, in emergency-settings, the diagnostic criteria suggested by Collins *et al.* [16] are different. In these contexts, wasted adults of both genders should be admitted to therapeutic feeding programmes when: their MUAC is below 160 mm, irrespective of clinical signs; or their MUAC is between 161 and 185 mm in association either with bilateral pitting oedema, or with inability to stand, or with apparent dehydration. According to the same authors, admission to adult supplementary feeding centres should be based upon MUAC between 161 and 185 mm. Table 2 compares the criteria to classify malnutrition in children and adults.

Table 2- Comparison of classifications of acute malnutrition (WFH, and/or oedema) and associated risk of death (MUAC) in children and adults.

Nutrition Indicator	Moderate Acute Malnutrition (MAM)	Severe Acute Malnutrition (SAM)
WFH (wasting)	≥ -3 SD & < -2 SD	< -3 SD
MUAC	≥ 115mm & < 125mm (≥ 11.5cm & < 12.5cm)	<115mm (<11.5cm)
MUAC for age/height[4]		< -3 SD
Bilateral Oedema	No	Yes

Nutrition Indicator	Moderate Acute Malnutrition (MAM)	Severe Acute Malnutrition (SAM)
MUAC (WHO 1995)	≥ 214 mm and ≤221 mm (women) ≥ 224 mm and ≤231 mm (men)	< 214 mm (women) < 224 mm (men)
MUAC (Ferro-Luzzi 1996)	< 190 mm (women) < 200 mm (men)	<160 mm (women) < 170 mm (men)
MUAC (SCN 2000)	< 185 and ≥ 160 mm plus clinical signs*	< 160 mm
Bilateral Oedema	No	Yes

* Clinical signs include inability to stand, evident dehydration and presence of oedema.

In the first and the second tables, the classifications refer to children with 6 months to 5 years of age and to adults. Source: Harmonized Training Package[5].

1.1.1.2 Stunting (chronic malnutrition)

Chronic malnutrition or stunting share some of the underlying causes with acute malnutrition. However, stunted children are identified only over a longer-term, because of limitations in the available diagnostic measurements. This form of malnutrition slows down growth and reduces essential cognitive development in the affected children. Their height remains evidently too short for their age.

It is commonly accepted[5] that, after 24 months from birth, this condition may become irreversible, and is likely to lead to stunted adults with reduced physical and cognitive capacity. However, some recent evidence suggest that stunting is not an irreversible condition. Prentice *et al.* [17] looked at early growth patterns in children from 54 resource-poor countries in Africa and Southeast Asia, and concluded that substantial height catch-up occurs between 24 months and midchildhood, and again between midchildhood and adulthood, even in the absence of any interventions. More evidence is urgently needed.

Height-for-age is the index used to identify stunting. Moderate stunting is defined by a

deviation, from the norm, which is lower than -2 SD and higher than, or equivalent to, -3 SD. Severely stunted children are identified when the same index is lower than -3 SD.

1.1.1.3 Underweight

Underweight is a general measure that captures the presence of wasting and/or stunting. It is therefore a composite indicator, reflecting either acute or chronic undernutrition without distinguishing between the two.

Children with severe or moderate underweight show a weight-for-age Z-score respectively lower than -3 SD, or included between -3 and -2 SD.

1.1.1.4 HIV and TB wasting

Wasting associated with an infection differs from undernutrition due to low food intake. The latter, as earlier defined, is related to nutritional or dietary causes, like reduced energy or nutrient intakes. This sort of malnutrition was called “primary” in order to differentiate it from “secondary” malnutrition, which is subsequent to an infection such as HIV and TB[18,19]. The latter are associated with the loss of appetite[20,21], which may also contribute to a reduction of food intake.

Severe acute malnutrition is an important risk factor for mortality among HIV-infected children living in resource-limited settings[22]. Complications like electrolyte disorders, micronutrient deficiencies, and severe infections are often associated with SAM in HIV positive children[22].

Anthropometry, measured in adults, is strongly correlated with survival in presence of HIV and TB wasting[23,24]. Paton *et al.* [25] observed that BMI < 17 kg/m^2 is significantly associated with higher adult mortality[25], even in patients initiating anti-retroviral treatment (ART).

However, no international agreement was found about BMI or MUAC cut-offs to define wasting syndrome associated with these infections. Moreover, very little evidence is available showing the presence of nutritional oedema associated with HIV and TB, at least in adults. In a recent study from Zambia[26], HIV positive and negative children were found, respectively, to be more likely to present marasmus or Kwashiorkor.

When treatment is available, ART side effects may be worse in malnourished than in individuals, who are normal from the nutrition status point of view. This may be because of the documented toxicity of ART[27]. The latter may affect their quality of life and their long-term survival[22]. Metabolic complications of ART include lipodistrophy, dyslipidemia, lactic acidosis, insulin resistance, and osteopenia[22].

1.1.1.5 Micronutrient deficiencies

Micronutrient malnutrition affects populations in emergencies and other settings. This form of malnutrition is a significant cause of morbidity, mortality, and reduced human capital[5]. Black *et al.* suggest that micronutrient deficiencies are responsible for most childhood deaths and often co-occur with stunting and/or wasting[1]. An inadequate dietary intake is often the main cause. But infections can often alter the micronutrient levels in the plasma, while reducing absorption of specific nutrients and increasing, as a consequence, their intake requirements[5]. Poor growth in under-fives results not only from a deficiency of protein and energy, but also from an inadequate intake of vital minerals, and vitamins[9,28]. The standards for micronutrients dietary requirements according to sex and age-group are available from the US Institute of Medicine, the WHO, the FAO, and the European Commission. WHO considers anaemia, iodine-related disorders and vitamin A deficiency among the main priorities[29]. That is so, in particular among populations depending on food aid.

In emergency settings, Seal and Prudhon[30] report that micronutrient deficiencies have been documented for years, especially in refugee camps where they were most frequently assessed. For these specific contexts, the authors suggest methods to monitor the micronutrient content of the diet, and to measure micronutrient deficiencies in humans, taking into account programming issues.

1.1.1.6 Low weight at birth

Infant weight at birth is strongly associated not only with their chances of survival, growth, long-term health and psychosocial development, but also with their mothers' health and their nutritional status[31]. There is evidence that less than 2.5 kilograms at birth is a severe health risk factor[31].

1.1.1.7 Overweight and obesity

Overweight and obesity are forms of malnutrition. Kuczmarski *et al.* [32] define overweight as

the “weight that exceeds the threshold of a criterion standard or reference value”. A review[33] found that the available “studies have used a wide variety of obesity definitions and cut off points”. However, most of them were based on BMI values[33]. For both forms of overnutrition, Table 1 provides the anthropometric definitions in use by the UN.

The European regional office of WHO[34] suggests that the cut-off points of the 2006 BMI-for-age reference for children, with less than five years, for the diagnosis of overweight and obesity were set as the 97th and the 99th per centile, respectively. For those aged five to nineteen years, overweight is defined as a BMI-for-age value over +1 SD and obesity as a BMI-for-age value equal to or over +2 SD. Adults, whose BMI is greater than or equal to 25 kg/m^2, are considered overweight, while if their BMI is at least equivalent to 30, they are considered obese[10].

After having defined malnutrition and its sub-forms, the following sections explore their prevalence at the global scale.

1.1.2 Prevalence of paediatric and adult malnutrition

Malnutrition is a global health issue, and the public health burden is not decreasing. In the last two decades, for instance, UNICEF reports that, in developing countries, the relative reduction of stunting was 28 per cent. However, due to population growth, the overall number of African children under 5 years old who are stunted has increased, from an estimated 43 million in 1990 to 52 million in 2008. Simultaneously, underweight prevalence decreased very little, with only 3 per cent reduction in Africa (28% in 1990) and 6 per cent in Asia (37% in 1990)[35].

Hill *et al.* [36] consider nutrition an “ascendant issue on global and national policy agendas in recent years, as a result of the global food crisis and growing recognition of the magnitude and consequences of these problems for human and economic development”. This was already reflected in universal recent policies such as the Millennium Development Goals and the Copenhagen Consensus[37,38], where nutrition-related topics appeared among the top priorities.

More recently, the World Bank advocated that nutrition should be repositioned at the top of the priority agenda[39], promoting the collaboration from a wide range of stakeholders. This alliance includes governmental, non governmental institutions, donors and the private

sector. The initiative called Scaling Up Nutrition, is currently engaged in raising an annual investment of USD 6.2 billion, needed to provide treatment to 3.5 million under five children affected by SAM or MAM[40].

1.1.2.1 Prevalence of Undernutrition

In 2012, the WFP policy document number 5 reports that "there are a staggering number of hungry and undernourished people in the world. About 1 billion are undernourished, while 2 billion suffer from micronutrient deficiencies"[3]. Among children under 5, 127 million are underweight[41] and 56 million suffer from wasting[1]. WFP reports also that "the 195 million stunted children are at higher risk of mortality and of suffering irreversible, long-term consequences" when compared with non-stunted children[3]. Almost 9 million child deaths every year, one-third of the total, are related to undernutrition, more than any other cause of mortality[1], while it can be argued that actual causes of death from clinically defined SAM are often not recorded by current disease classification.

In 2008, in a special issue of the medical journal The Lancet, Black *et al.* [1] confirm the dramatic size of undernutrition and the related consequences. The data were based on 388 national surveys from 139 countries[1]. The global prevalence of underweight, stunting, and wasting among children below 5 years of age, were based on the WHO Child Growth Standards released in 2006. Of the 556 million children under 5 years of age in low-income countries, 20 per cent (112 million) were underweight, 32 per cent (178 million) were stunted, and 10 per cent (55 million) were wasted, including 3.5 per cent (19 million) who were severely wasted. Thus, about 36 million children are suffering from moderate wasting.

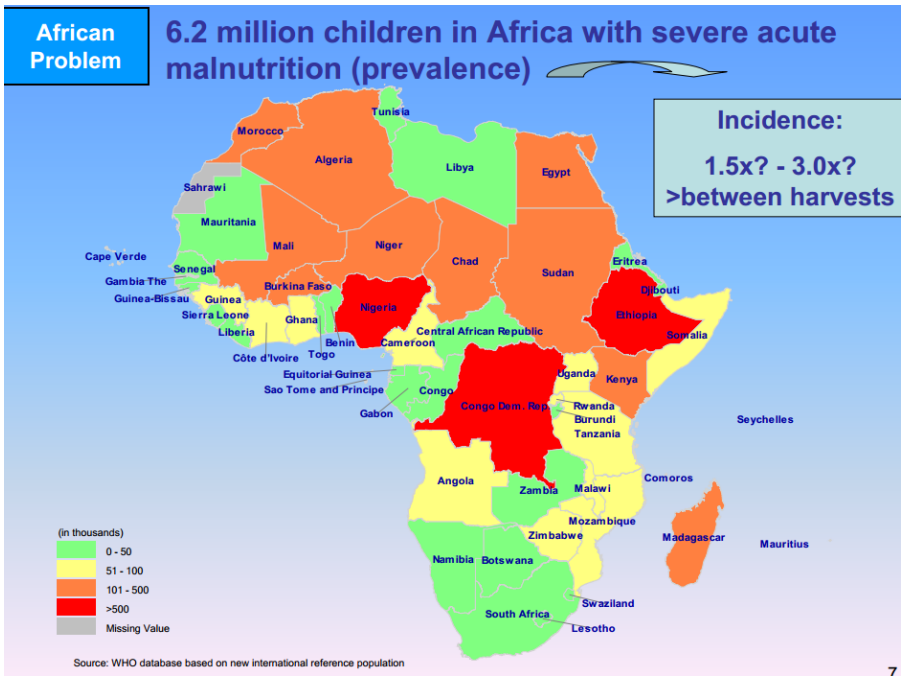
The impact of undernutrition was also estimated. Maternal and child undernutrition is the underlying cause of 3.5 million deaths every year, 35 per cent of the disease burden in children younger than 5 years and 11 per cent of total global disability-adjusted life-years (DALY)[1]. The DALY is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. Stunting, severe wasting, and intrauterine growth restriction together are responsible for 2.2 million deaths, and 21 per cent of DALY for children younger than 5 years[1]. This is "the largest per centage of any risk factor " in this age group[1].

Undernutrition has an impact on the economy of affected countries. Child undernutrition costs poor economies USD 6.7 billion, or more than 6 per cent of their GDP [42]. Of this total,

90 per cent is caused by higher death rates and lower education levels[42].

Human immunodeficiency virus contributes to increase mortality among undernourished children. A systematic review and meta-analysis[43] explored HIV prevalence and mortality in

Figure 3 - Prevalence of severe acute malnutrition in Africa.



children undergoing treatment for SAM in sub-Saharan Africa. In this study, among children from 17 feeding programmes (n=4,891), 29.2 per cent were HIV-infected and they were more than three times more likely to die than HIV-uninfected children[43].

Less evidence is available to define the size of prevalence among adolescence and adults. However, recent studies[23,44–49] report that HIV/TB wasting in adults is a public health issue in Sub-Saharan Africa, in spite of the increasing access to ART. Uthman *et al.* [44] report that demographic and health surveys from 11 sub-Saharan African countries estimated that 10.3 per cent of HIV infected women (aged 15-49 years) had BMI lower than 18.5 kg/m^2. Furthermore, severe wasting was found in advanced stages of the disease. For instance, in urban Lusaka, Zambia, 9, 8 and 17 per cent (n=40,778) of people initiating ART were found with a BMI lower than 16.0, 16.0 to 17.0, and 17.0 to 18.5 kg/m^2 respectively[45].

Undernutrition is also prevalent among older people. Whereas the population of the world

is ageing, undernutrition amongst individuals in this life-stage is a global crisis, and set to increase[50]. Visvanathan suggests[50] that malnutrition is due to decreased intake and weight loss, both in low and in high-resources settings. At present, almost 44 per cent of healthy, community dwelling, older people in developed countries are at risk of malnutrition[51]. More precise figures are missing in countries with low-income economies.

1.1.2.2 Prevalence of undernutrition in presence of overnutrition: the double burden effect

According to WHO[10], worldwide obesity has more than doubled since 1980. In 2008, 1.5 billion adults, 20 years and older, were overweight. Among these, over 200 million men and nearly 300 million women were obese[10]. Nearly 43 million children under the age of five were overweight in 2010[10]. However, obesity is preventable[10].

The same WHO document reports that many low- and middle-income countries are now facing a "double burden" of disease. Infections and undernutrition co-exist with a rapid upsurge in “non-communicable disease risk factors”, as obesity and overweight are currently called. Initially, this seemed particularly true in urban settings[10]. However, recent evidence shows that rural areas are also increasingly affected[52]. Therefore, finding undernutrition and obesity existing side-by-side within the same country, the same community, and the same household has become less uncommon.

In both poor and large economies, children are more prone to follow inadequate food habits[10]. High-fat, high-sugar, high-salt, energy-dense, and micronutrient-poor foods tend to be lower in cost. When these come together with low levels of physical activity, obesity syndrome becomes evident. However, unmonitored distribution or uncontrolled marketing of food aid items with high energy density and sugar content may represent similar public health risks.

The previous sections of this thesis reported the staggering prevalence of the existing forms of malnutrition, in particular of undernutrition. The following part describes how the latter is managed.

1.2 Management of undernutrition

The management of undernutrition is complex. This is because it requires a combination of

methods, specific for its forms, degrees and settings. Briony *et al.* [53] define the management of undernutrition as a "graded process of increasing levels of intervention". These include "improving energy and nutrient intake from ordinary foods; fortifying the energy and nutrient intake of food and other forms of supplementation; enteral nutrition; and parenteral nutrition". These approaches are routinely applied in high-resources settings.

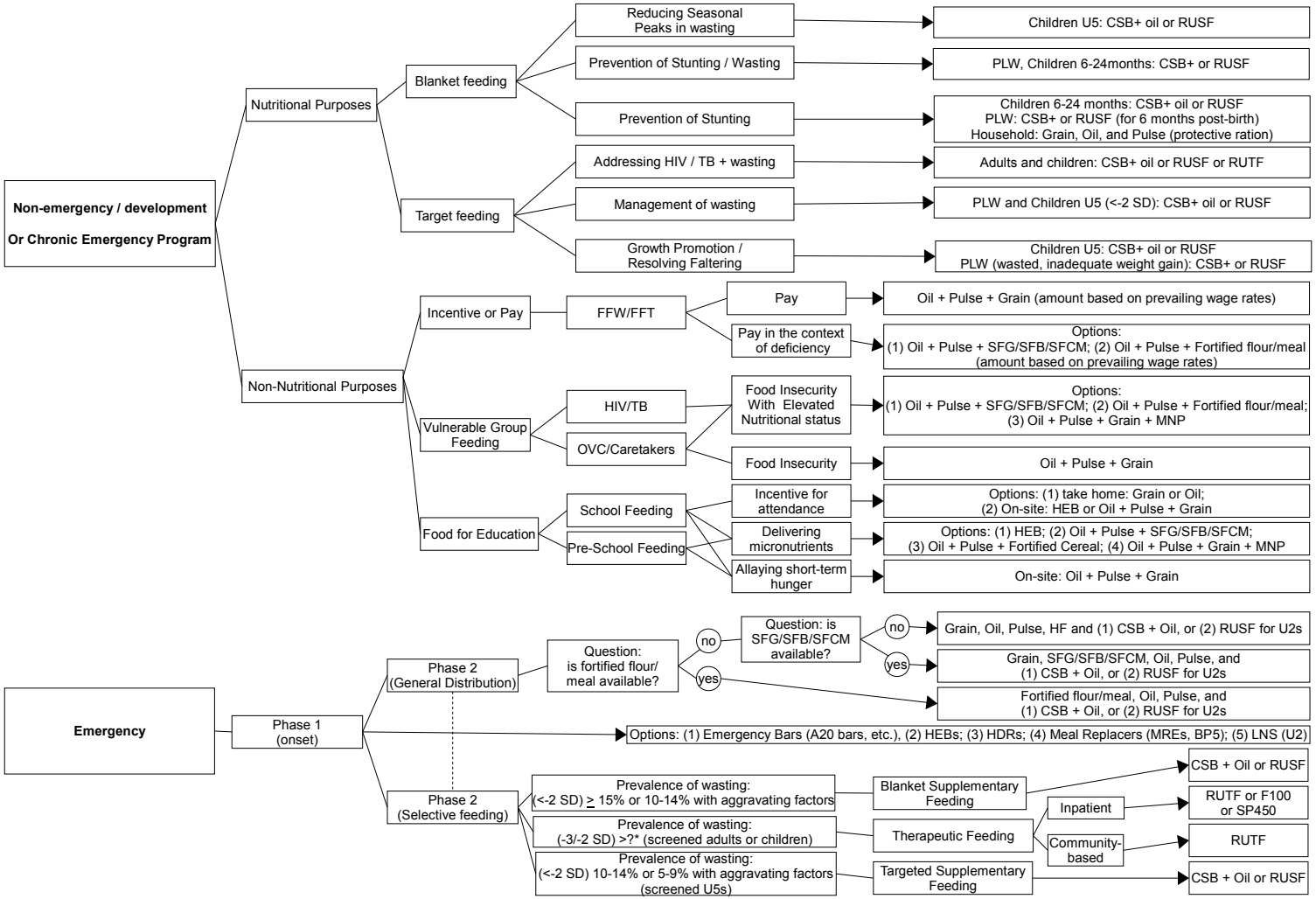
Undernutrition tends to be more common in low-resources settings. But here, its management is often more challenging. For this reason, food-based programmes were often tailored according to three main situations: (i) non-emergency /development, (ii) emergency and (iii) chronic emergency contexts.

In recent years, the USAID, the UN Nutrition Cluster, UNHCR, and WFP suggested, for these specific settings, which type of programme and food commodities are more adequate. However, it was concluded that "there is no one food product that can meet every kind of programming goal, and no one programming approach that fits all needs"[54].

In 2011, USAID[54] in collaboration with members from WFP and other institutions developed a flow chart to help policy makers and donors in taking more informed decisions about programmes and choice of food-products. The flow chart, available in Figure 4, describes how the "non-emergency/development" and "chronic emergency" contexts rely on programs using food "primarily for explicit nutritional" or "non-nutritional purposes". Emergency contexts may require general or selective distribution according to local availability of food aid items, wasting prevalence, timing issues and logistic constraints.

In summary, despite the complexity of this decision tool, the large variety of food aid products and their vast number of combinations is rather evident.

Figure 4 - Flow-chart for the choice of food aid items.



Note: BP-5 Compact food; CSB, Corn-soy blend; FBP, Food by Prescription; FFE, food for education and child nutrition; FFT, food for training; FFW, food for work; HDR, humanitarian daily rations; HEBs, High-Energy biscuits; LNS, lipid-based nutrient supplement; MCHN, Maternal and Child Health and Nutrition; MNP, Micronutrient powder; MREs, meals ready to eat; OVC, orphans and vulnerable children; PLW, pregnant and lactating women; PM2A, Prevention of Malnutrition in Children Under Two Approach; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food; SFB, Soy-fortified bulgur; SFCM, soy fortified corn meal; SFG, soy-fortified grits; U2, under 2 years of age; U5, under 5 years of age. Source: USAID 2011[54]. * The minimum prevalence value was missing.

Each branch of the flow chart informs practitioners and donors, involved in large feeding programmes, of the ration and food adequate choice. For emergency contexts, the diagram helps in choosing packaged products used to promote survival, while preventing starvation. This is valid for phase 1 of emergency onsets, whereas in phase 2, choices are made based on the availability of food products and prevailing nutrition situation (general food distribution and selective feeding).

The choice of the food-items is relatively large, and includes processed and non-processed commodities. The programmes designed with explicit nutritional purposes (Figure 4) mainly use two groups of processed food products: fortified blended flours (FBF) and lipid-based foods, both fortified.

In the first case, flours based on corn, soy, bulgur, or wheat are blended into formulations, first fortified with micronutrients, then cooked into a porridge. The second category of products includes “safe, palatable foods with a high energy content and adequate amounts of vitamins and minerals”[55]. Therefore, it can be argued that the convenience in the latter group may often be higher than in the former.

For this reason, some of them are increasingly used in therapeutic, or supplementary feeding programmes. The following sections of this thesis explore in detail their importance. However, the current methods and protocols stand on the shoulders of previous pioneering research and their applications, including their successes and failures. Their value, therefore, deserves to be recognized, and their evolution described. The following section retraces the history of the current therapeutic and supplementary feeding protocols to treat undernutrition and its acute form.

1.2.1 Evolution of the management of undernutrition

Undernutrition is as old as history itself. Its descriptions fill an undocumented number of pages in the literature of mankind. And yet, in the era of modern medicine, its management has had a relatively short, but interesting evolution.

Figure 5 - The Jamaican Paediatrician Cecily Williams (1893 -1992).

Source: reference number [482].

The Jamaican paediatrician Cecily Williams is probably among the first ones to describe, in a peer-reviewed journal published in English language, a specific form of undernutrition, and to suggest its treatment. In 1933, her article[56] reports:

"There is a well-marked syndrome, not uncommonly found among the children of the Gold Coast Colony (Ghana), which I have not found described.

…The syndrome consists of oedema, chiefly of the hands and feet, followed by wasting; diarrhoea; irritability; sores, chiefly of the mucous membranes; and desquamation of areas of the skin in a manner and distribution which is constant and unique".

The description suggests that the disease:

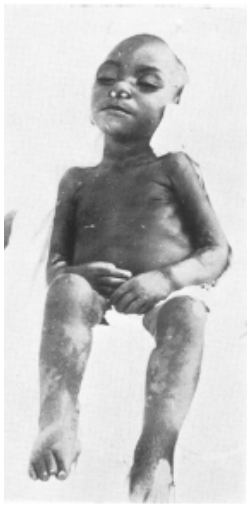
"…appears to be due to some dietetic deficiency and to be uniformly fatal unless treated early".

The management of the condition was also described:

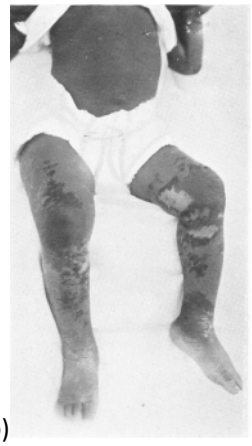
"…My general impression is that the most important elements in the treatment adopted were cod-liver oil and a good brand of tinned milk".

Figure 6 - The first pictures of a dietetic disease (Kwashiorkor) never described before on a medical journal.

(a)



(b)



The original captions of photo (a) and (b) report "case 2 and 3 after their death". Source: Williams *et al.* (1935)[56]

Two years later, from the pages of The Lancet journal, Williams names this disease “kwashiorkor”. In the Ga language, coastal Ghana, the term means "the sickness the baby gets when the new baby comes". From the perspective of the local population, the expression describes the cause of the condition in an older child, who has been weaned from the breast, when a younger sibling comes.

In the following decades, other authors described undernutrition in very large populations. Ancel Keys, in 1945, is probably the first author who describes the physiology of starvation in volunteers[57] with a modern medical perspective[9].

Since then, new evidence has filled the existing knowledge gaps in undernutrition, to improve its treatment and, later on, to support the up-scaling of its prevention programmes. The historical development of the management of acute malnutrition is summarized in Table 3, and described in detail in the next five sections.

1.2.1.1 Phase 1: the theory of protein-energy malnutrition and the role of infections (1933-58)

The relationship between status of undernutrition, its dietary treatment and infections has been a topic of study for much of the 20th century[58]. In 1933 and 1935, Williams[56,59] first described Kwashiorkor in Africa, which was also found later (1954) in Latin America[60]. But already in 1950, Keys described the link between the disappearance of famines with the population returning to a normal diet[61]. In Europe, Marasmus was described during and after the Second World War[9].

The treatment based on this early classification of undernutrition was based on diets high in both protein and energy[9]. From this perspective, Protein-Energy Malnutrition (PEM), was “attributable principally to dietary deficiencies and therefore it could be prevented or treated by dietary measures alone”[58]. “Children were then admitted to large inpatient feeding centres based on their arm circumference for height or for age, and then treated with a mixture of dried skimmed milk, oil, and sugar, diluted into clean water”[62] .

Based on this approach, the effectiveness was limited, and the mortality still high, according to narrative studies (data not reported)[58]. The understanding of the cause was insufficient,

and Keusch argues that was due to little exposure of human nutritionists to immunologists or infection specialists[58]. This type of management continued to be common during the next few decades.

In his "history of malnutrition, infection and immunity", Keusch[58] calls the years preceding 1959 "the dark ages". In that year, for the first time, Scrimshaw, Taylor and Gordon[63] describe the "powerful pathway" of "the cyclical interactions between malnutrition and infection". This consisted of a "cycle of malnutrition-infection, more nutritional deterioration-more infection"[58]. From this perspective, improving nutritional intake was insufficient to fully reverse this cycle. That was due to the presence of repeated exposure to infections, highly prevalent in developing countries. Keusch highlights how only then it became clear that "a dual attack on nutrition and infection was needed for an optimal response".

Table 3 - Evolution of the management of acute malnutrition since 1933.

Knowledge gap	Achieved knowledge (type of study)	New management protocol based on:	Source
Phase 1: 1933-1959			
The scientific evidence to manage acute malnutrition and to reduce associated case fatality rate is limited	Malnutrition is attributed to a deficiency in protein and energy (observational) Infections and undermined immunological response worsen undernutrition status (observational)	High protein and energy diets in association with medical treatment	Williams[56], Scrimshaw *et al.* [63]
Phase 2: 1960-1989			
In SAM, the case fatality rates remain high, and the causes are not understood	Untreated water and mother "ignorance" are recognized as other main causes of case fatality	Additional rehydration protocols, water and sanitation operations, and educational programmes	Beaton & Ghassemi[64]
Phase 3: 1990-1999			
Case fatality rates remain high and, in people nutritionally rehabilitated from SAM, protein-related metabolic dysfunctions are observed, but not explained	The roles of appetite and type I / II nutrients explain protein-related dysfunctions (physiology-based observational) Nutritional requirements, tailored for treatment of SAM are proposed, (observational), and their dietary application (therapeutic milk formulas) increases the survival rate in treated groups (observational)	Additional protocol consisting of 10 consecutive steps, in in-patient settings, and introducing F75 & F100 milk formulas Impact assessment focusing on recovery and survival rates	Brown *et al.* [65,71], Golden *et al.* [66–69], WHO[70]
Phase 4: 2000-2007			
In home-based care, the setting conditions are inadequate limiting the application of the 10-steps protocol, early admission of children with SAM is difficult, programme coverage levels are relatively low, and viable alternatives are needed	The combination of community involvement, MUAC, and RUTF, is suitable for home-based treatment of GAM (observational), increases early recruitment of cases both with (in-patient programme) and without (out-patient) medical complications (observational), and improves programme coverage levels (case-control and observational) In controlled conditions (RCT) a RUTF-based regime increases daily energy intake and weight gain, shortening the rehabilitation time of children affected by SAM	An additional protocol, integrating in- and out-patient care, focusing on community involvement, early diagnostics (MUAC), and weekly supply of RUTF for supplementary and therapeutic feeding, drugs and medical check ups An impact assessment focusing predominantly on coverage	Diop *et al.* [71], UN Joint Statement[55], Myatt *et al.* [72], Myatt *et al.* [73]

Knowledge gap	Achieved knowledge (type of study)	New management protocol based on:	Source
Phase 5: 2008-2011			
The prevalence of SAM among children under 6 months of age, and the nutritional and dietary requirements for MAM and for wasting syndromes associated with HIV are unknown	The burden of SAM in children under 6 months of age is high (data review), and recommendations for treatment are urgently needed Nutritional and dietary requirements for treatment of MAM in children are proposed (literature review) Recommendations for treatment of HIV wasting are recognized to be urgently needed (literature review)	Improved protocols include RUSF and specifically designed fortified blended flours, as part of food aid options Evidence-based guidelines for treatment of children under 6 months of age with SAM, and for adults living with HIV are missing or insufficient	Golden[28], USAID[54], Kerac *et al.* [74], Forrester *et al.* [75]

1.2.1.2 Phase 2: the disillusion

Even if reducing infections, the new protocol to treat undernutrition caused physicians like Srikantia[76], and Gopalan[77] to be perplexed about its results. Their work launched the base for the recognition that, in SAM, child recovery based on large protein intakes remained inadequate. They described the increasing evidence[78–84] that once rehabilitated, the children still "suffered from liver dysfunction with reduced levels of" enzymes metabolizing amino acids, and "abnormal urinary" catabolites. Soon after McLaren summarizes the same findings in the publication called "The great protein fiasco"[85], which marks the conceptual shift from Protein-malnutrition to Protein-Energy malnutrition.

Later on, it became clearer that the treated children were unable "to return to be normal"[9]. This was reflected in post-recovery compromised renal functions, glucose intolerance, and abnormal insulin secretion[86–88]. While the causes remained undisclosed, the wording "protein-energy" started to seem "inappropriate"[9] to describe the complexity of the treatment required.

However, it was only in 1982, after at least two decades, that the partial failure of the PEM approach in saving lives was fully recognized. Beaton and Ghassemi[64], looking at 200 reports from high-protein, high-energy feeding interventions around the world, found that "the programs reviewed were not effective"[64], that "preventing 'less-than-severe' malnutrition was not clear"[64] and that "the observed growth response accounts for only a small part of the net increase in energy intake"[64].

In a personal communication (September, 2012), Tomkins suggested that at that time, Jamaica was one of the few countries having enough resources to adequately study metabolic problems associated to PEM. In addition to this, here mortality due to SAM was rare.

However, the disillusion about the poor results, derived from the PEM approach, led the decision makers to focus on two aspects: the clinical aetiology as primary cause of malnutrition, reinforcing the role of the infections, and the theory that "mothers are ignorant and that education is the main intervention required"[9].

Policy makers promptly responded and produced policies accounting for these two

elements. Soon after, in low-resources settings, large programmes to improve water access and sanitation became more common than ever[9]. Golden[9] finds that this approach is still present in the recent Lancet series, in 2008.

Although known and accepted long before (personal communication: Tomkins, September 2012), decision makers waited until 1989, before evidence emerged that that the reduction of diarrhoea due to sanitation interventions may be too small to have a large impact on malnutrition by itself[89], and that, most of all, "mothers were not to blame"[9]. More recently, the Lancet Series on Nutrition (2008)[90] still promote handwashing-interventions despite the controversial available evidence on their favour in promoting children growth.

1.2.1.3 Phase 3: appetite and the theory of type I and II nutrients

In the meantime, since the early 80's, important physiological studies, focusing on appetite, highlighted the new steps to take to move on.

Evidence showed that "appetite is a measure of metabolic wellbeing". Moreover, appetite was found to be "particularly disturbed with livery dysfunction during the metabolic response to infections"[65], but, most of all, by the deficiency of certain essential nutrients[9]. Pioneering studies conducted in Jamaica[65,91], looking at the treatment of severely malnourished children, confirmed this relation. The impact of this discovery is emphasized by Golden[9]:

> *…dietary surveys will indeed show that they (children with SAM) have a reduced energy intake, but this will not be due to energy deficiency and not be corrected by giving additional energy in the form of carbohydrate or lipid.*

Golden continues saying that severe malnutrition…

> *…will only be cured by giving the specific nutrients that are missing in the habitual diet that cause the loss of appetite.*

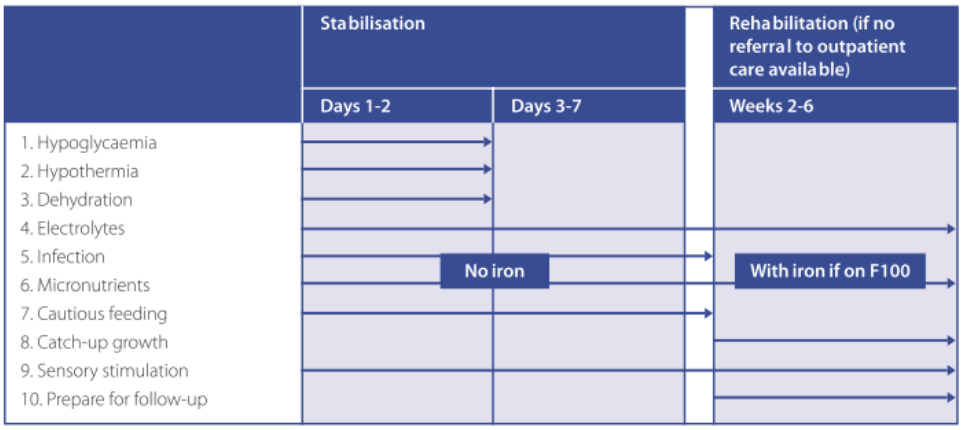
The role of the appetite and the specific elements increasing survival in starving individuals merged into the theory of "type I and II nutrients". This theory, formulated, systematized and published[66–69] in the early years 90's, is still considered valid by many nowadays[28], although it does not explain the severe anorexia seen in the presence of infection.

The theory proposed by Golden suggests that nutrients called type I (see their list in foot note number[1]) are "needed for particular biochemical functions in the body"[28]. Deficiency of these nutrients does not generally lead to growth failure[28]. On the other hand, "type II nutrients (foot note[2]) are likely to become *limiting* in the diet before the protein"[9]. "If the diet is poor, then when weight is lost from an infection, there will be insufficient type II nutrient density to allow for catch-up growth during convalescence"[9]. The resurgence of appetite is an indicator that the type II nutrient balance has been re-established.

The theory was soon applied. In 1989, the type I and II nutrients theory was behind a "factorial approach to design a diet that would provide all the building blocks for re-synthesis of normal body tissues"[9]. The diet showed to be rather successful[92], becoming the foundation of the current protocol for in-patient treatment of SAM[70].

Box 3- Guidelines for the inpatient treatment of severely malnourished children

The WHO 1999 protocol to treat SAM is based on the F75, and the F100 milk formulas, used in combination with ten activities, summarized as follows:



Adjusted by HTP 2011[5] from WHO 1999[70].

The nutrient profile of the diet was soon replicated in an industrially processed therapeutic milk, called F100 (formula with 100 kcal/ml). In 1993, F100 was successfully clinically tested in emergency settings. However, the F100 formula had to wait for 1999 to become part of

[1] Namely: calcium, iron, copper, selenium, iodine, vitamin B1, B2, B12, C, E, A, and K, niacin, pyridoxine, folic acid, biotin, pantothenic acid, manganese, chromium, molybdenum, fluorine and essential fatty acids[28].

[2] Namely: protein, sulphur, potassium, magnesium, phosphorus, and zinc[28].

the WHO guidelines to treat SAM in children, adolescence and adults[70].

The WHO protocol also included the use of a second formula milk, termed F75 (75 kcal/ml), who's energy density was lower when compared to F100.

In the WHO protocol[70], the complete treatment is composed by ten steps organized in two phases. The first, called Stabilisation phase, based on the F75 formula, re-establishes the full functionality of the metabolism, resulting in the re-appearance of appetite. Once the appetite is confirmed to last at least few days, the following Rehabilitation phase aims for the full recovery of weight gain. The steps and their sequences are detailed in Box 3 and are based from the extensive research work conducted in Jamaica.

Briend and Collins[62] suggest that "with these new dietary protocols and relatively intensive medical care, recovery rates improved, often exceeding 75 per cent ", and that "mortality rates were reduced to below 10 per cent "and that, from a clinical perspective, "these protocols were considered as rather successful".

The protocol showed, however, two major constraints. This regime could treat only people in in-patient programmes. F100 is a liquid milk-based diet, it is prone to contamination, and "it can be used exclusively in health facilities to prevent misuse"[9]. Because of this reasons, the life of large numbers of starving people, living far from clinic facilities, could not be saved. Golden recognizes that "in many settings it is not possible for mothers to leave their families for extended periods, or to travel long distances"[9]. Other authors[62] suggested that "this was especially the case in open situations amongst dispersed communities living in chronic poverty, where often specialized inpatient feeding centres were not accessible. In their absence, children had to be referred to overcrowded paediatric or general wards ill-equipped to give adequate care to malnourished children. Having the mother staying with the child for several weeks was also a major problem when they were engaged in agriculture or other life sustaining activities".

In poor settings, health staff struggles to correctly implement the WHO 1999 guidelines. In 1996, Schofield and Ashworth[93] reported that "the median case fatality from SAM has remained unchanged" (20 to 30 per cent), "with the highest levels (50 to 60 per cent) being among those with oedematous malnutrition". The cause is likely due to "faulty case-management"[93], because in health facilities of poor countries, the work load of nurses and doctors is often overwhelmed by the large number of patients, the health equipment often

is not maintained in function, and the hygienic conditions are limited by overcrowded wards. The same authors conclude that, in such contexts, rigorously implementing the WHO 1999 protocol proved to be challenging[93].

Therefore, in spite of the achievements based on F75 and F100 formulas, Collins and Briend[62] polemically argue that "between 1950 and 2000, efforts to treat these children as inpatients in district hospitals or clinics failed to address" this public health burden.

1.2.1.4 Phase 4: large coverage, high recovery, and low mortality

At the beginning of the new millennium, an innovative product was tested. A derivative of F100, in the form of a paste, called ready-to-use therapeutic food (RUTF), allowed mothers, living far from the health facilities, to treat their severely malnourished children directly at home, whenever there was no medical complication. Mobile clinics provided a weekly medical check-up for the child, and supplied the mother with RUTF, counselling and training. These visits followed a schedule which was previously agreed together with the community leaders.

The main ingredients in RUTF were peanut, milk powder, oil, sugar, fortified by a premix of vitamins and minerals. The brand name of the first RUTF was Plumpy'Nut, and was produced initially in France by the manufacturer of F100, called Nutriset. Since then, the number of manufactures has increased. In 2012, Komrska[94] reports that twelve suppliers were approved by the UNICEF Supply Division to produce and distribute RUTF at a global level.

The evidence behind RUTF effectiveness was robust. In 2003, in a RCT conducted under strict direct observation in a Senegalese health facility[71], children with SAM showed a significantly higher daily energy intake, faster weight gain, and a shorter treatment duration when treated with RUTF compared with F100. Cases fatality (2 out of 30 children) was reported only in the F100 study arm.

Based on the contribution from previous studies on home-based care models, conducted in Bangladesh[95] and Jamaica[96], a few years later, the first protocol based on RUTF was released and named "Community-based Therapeutic Care"[97]. Similar, home-based approaches were developed by a number of NGOs, including MSF and ACF. In 2007, the UN endorsed home-based treatment of SAM with a new name: "Community-based Management of Acute

Malnutrition" (CMAM)[55]. In the following years, CMAM becomes a mainstream activity in humanitarian feeding programmes, treating large populations in Africa, in Asia and in Central America (Haiti) affected by SAM.

Briend and Collins[62] emphasize that "when the model was endorsed by the UN, mortality rates had been reduced to less than 5 per cent "[98] and that "by 2009, all major relief agencies and 25 national governments had formally adopted this new model". In 2010, "approximately one million cases of SAM were treated annually, with programs expanding by approximately 30 per cent every year"[62]. The same authors summarized the CMAM protocol in the following way:

i. *"the introduction of techniques to engage with communities to promote early presentation and compliance;*

ii. *handing over the identification of SAM to the community through the use of MUAC;*

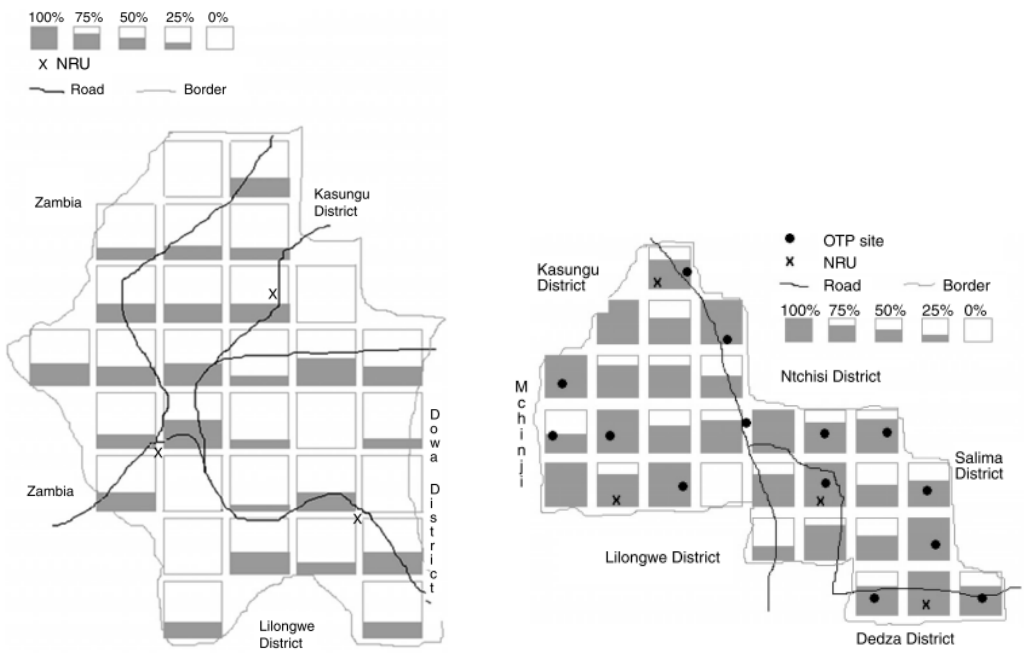
iii. *the development of Ready to Use Therapeutic Foods (RUTF)."*

The previous and the new models to treat acute malnutrition are complementary. The previously described model to treat SAM, based on F75/F100, becomes one of the components of the new model (CMAM), which includes also the use of RUTF. The criteria based on medical complications and appetite determine the admission to one of the two programme approaches. Children with medical complications and little appetite are referred to in-patient programmes[97] which follow the WHO 1999 protocol and where therapeutic formula milks are used. With the successful treatment of the medical complications, and the return of their appetite, children are discharged from the in-patient programme, enrolled in the out-patient programme, and treated with RUTF. Children initially presenting no medical complication and appetite are directly enrolled in the out-patient programme and treated with RUTF at community-level. Children already in the out-patient programme, presenting medical complications and/or low appetite, are admitted, or re-admitted, into the in-patient programme and follow the same rehabilitation path. Children discharged from the severe phase of CMAM/CTC, are admitted to a supplementary feeding programme, if one is operating, until complete recovery.

The CMAM/CTC approach is efficient in reaching cases of SAM even when located far from the in-patient facilities. An indicator called “coverage” measures this aspect of programme performance, and in this new phase of the management of SAM, the concept of programme coverage received emphasis like never before. The Sphere Project[99] defines coverage as the number of “individuals who *need* treatment, against those actually *receiving* treatment”. Coverage can be affected by the “location and accessibility of programme sites”. In the current guidelines for feeding programmes coverage is expected to be above “50 per cent in rural areas, 70 per cent in urban areas and 90 per cent in a camp situation”[99]. In 2010, Guerrero suggested that “the impact of public health nutrition programmes is determined by a combination of recovery and coverage rates”[100]. However, after a few years, the importance of coverage increased and some authors argue[72] that “a high coverage programme with a low cure rate may be better at meeting need than a low coverage programme with a high cure rate”.

In 2007, a study in Malawi[72], comparing two interventions, the first based on F75/F100 (WHO 1999 guidelines) and the second one on RUTF (CMAM 2007), found that the latter

Figure 7 - Spatial distributions of per-quadrat coverage in two feeding interventions (Malawi).



In the first map (Mchinji district), the protocol to manage SAM was based on WHO 1999. In the second map (Dowa district), the protocol was based on Community-based Management of Acute Malnutrition 2007 guidelines. The “x” and the acronym NRU correspond to nutritional rehabilitation unit, whereas OTP stands for out-patient therapeutic programme.

"enabled higher impact on severe malnutrition in this population". The first programme reported 24.5 per cent and the second 73.6 per cent of the children in need enrolled in each of the two programmes. Figure 7 compares the differences between the spatial distributions of coverage for the two programmes.

In the following year, further evidence confirmed the efficacy, the safety and the cost-effectiveness of RUTF in uncomplicated SAM. In 2010, a systematic review[101] for home-based therapeutic nutrition found 7 observational trials. The review concluded that "RUTF was at least as efficacious as F-100 in increasing weight and more effective in comparison to home-based dietary therapies". The combined results showed that recovery rate, mortality and default in treatment with RUTF were 88.3, 0.7 and 3.6 per cent, respectively with a mean weight gain of 3.2 g/kg/day. In Lusaka, Bachman[102] found that the use of RUTF in a "Community-based Therapeutic Care for SAM appears highly cost effective". The primary outcomes were mortality-within-one-year, and disability adjusted life years (DALYs) after twelve months survival.

In only a few years, after the RCT study undertaken in Senegal (2003), RUTF was not only used to manage cases of SAM, but even to prevent them. In the drought of year 2006, in western Africa, MSF tentatively extended the use of RUF to moderately malnourished children. The intervertion reported high cure and low default rates, compared to results typically obtained with the standard treatment of moderate malnutrition with fortified blended flours[103,104]. The use of RUTF for moderately malnourished children flattened the typical seasonal rise of admissions in SAM feeding interventions.

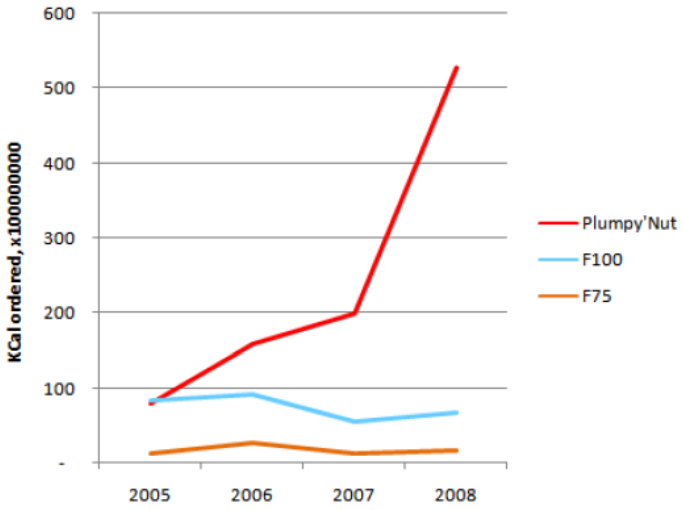
Cost is often a limiting factor in humanitarian interventions based on selective targeting. This is because the latter is more resources intensive. Blanket supplementary feeding programmes may be cheaper and in some cases relatively easier to implement. For this reason, in the same study, but in the following year (2007), MSF explored "whether it would be more feasible and effective to aim for blanket coverage with a nutritional supplement, which could prevent the development of stunting and wasting"[104]. Therefore, a new ready-to-use food (RUF), developed as a child diet supplement was distributed during six month, during the 2007 year hunger gap, in a district of Niger. Sixty-thousand children received the product, and "the incidence of severe acute malnutrition (MUAC<110 mm) remained at extremely low levels". Moreover, 92.3 per cent of the children were successfully treated,

with a weight gain of 5.1 g/kg/d, and only 1.8 per cent suffered from a fatality case (death).

This operational research and intervention strategy attracted some criticism. Latham *et al.* reacted, urging that the prevention of malnutrition should not be based on an industrially processed product, but on the eradication of the causes, and suggesting that the use of "RUTF would be a catastrophe", since it would be responsible for displacing breastfeeding practices[105].

The latter issue was supported by little evidence. The following year, in the Democratic Republic of Congo, one RCT study[106] assessed "the breast-milk intake of 9 to 10 month old infants given either a ready-to-use complementary food (RUCF) paste or a standard corn-soy blend porridge" commonly used in the complementary feeding phase. The technique used was based on a "deuterium-dose-to-the-mother dilution". No differences in breast-milk intake were observed between infants consuming either RUCF or the porridge. A second RCT study[107], in rural Malawi, found similar results. In children of similar age, twelve-month-long complementary feeding with 50 g/d of a RUTF-like product was significantly more likely to have a positive and sustained impact on the incidence of severe stunting, than with a maize-soy flour. Also in this case, the breast milk intake did not differ in the two groups.

Figure 8 - Nutrition commodities ordered by UNICEF country offices (in Kcal).



Source: UNICEF / Duke University 2009 [119].

In spite of this evidence, the debate about the use of lipid-based RUF remains. In 2011, the World Public Health Nutrition Association (WPHNA) voiced deep concerns about the future risk, associated with these products, of increasing the global phenomenon of the dual burden[108], described in section 1.1.2.2. The same year, within a public-private partnership,

both in developed and less developed countries, USAID in collaboration with WFP provided important recommendations[109] in order to improve the distribution, the targeting and the marketing of these and other food aid items. The concerns raised by WPHNA were not included in the recommendations.

1.2.1.5 Phase 5: scaling-up the procurement of low-cost, evidence-base RUF to treat other forms of malnutrition

At the end of the first decade of the third millennium, the use of RUTF is increasing exponentially (Figure 8). At the same time, this and novel formulations are being tested for the treatment of other forms of malnutrition. This section describes the scaling-up of the demand of RUF and summarizes which other forms of malnutrition RUF are increasingly used for.

In 2009, Ashworth and Ferguson[110] reported that beside MSF, the NGO GOAL also distributed "RUTF for moderately malnourished children with medical complications", while some UNHCR and UNICEF programmes provided "RUTF for moderately malnourished children with HIV".

Table 4 - Procurement of RUTF by UNICEF country programmes in 2003-8 (over 100 MT).

COUNTRY PROGRAMME	QUANTITY (MT)
UNICEF-Niger	1759
UNICEF-Ethiopia	1673
UNICEF-Sudan	854
UNICEF-Burkina Faso	528
UNICEF-Somalia	509
UNICEF-Burundi	351
UNICEF-Kenya	343
UNICEF-DR Congo	272
UNICEF-Mozambique	237
UNICEF-Kenya (for South Sudan)	213
UNICEF-Mali	201
UNICEF-Togo	199
UNICEF-Eritrea	193
UNICEF-Uganda	171
UNICEF-Mauritania	147
UNICEF-Madagascar	135
UNICEF-Chad	133
UNICEF-Afghanistan	115
UNICEF-Angola	110

Source: UNICEF (200?).

An undocumented correlation exists between the rise of evidence-based positive outcomes in RUTF-related programmes[72,107,111–118], and the steep increase of its demand. This can be also associated with the role played by UNICEF and MSF as described in section 1.3.3 of this chapter. A study[119] commissioned by UNICEF reported that the market for RUTF "had been growing steadily throughout the decade" and had "more than doubled in the year following the UN joint statement (2007)". "Production capacity of RUTF also increased, but at times has not been able to keep pace with rising demand" (Figure 8). In 2010, Yach *et al.* [120] confirmed that global "demand for a high-quality, safe, and nutritious RUTF is not being met".

Table 5 - Countries with reported SAM percentage for which UNICEF has not procured RUTF in 2008.

Bangladesh (13)	Jamaica (4)	Philippines (6)
Cambodia (7)	Kyrgyzstan (4)	Rwanda (4)
Cameron (6)	Lao (15)	Sao Tome and Principe (8)
Cuba (2)	Lebanon (5)	Surinam (7)
Ecuador (2)	Maldives (13)	Thailand (4)
El Salvador (4)	Mexico (2)	Macedonia (2)
Equatorial Guinea (7)	Moldova (4)	Trinidad and Tobago (4)
Gabon (3)	Mongolia (2)	Turkmenistan (6)
Gambia (6)	Montenegro (3)	Uzbekistan (3)
Guyana (11)	Morocco (9)	Venezuela (4)
India (20)	Nicaragua (2)	Vietnam (7)

The figures in parenthesis report the average percentage of children suffering from global acute malnutrition in period 2000-2006 [483]. Source: UNICEF 2008 [121].

In 2008, UNICEF released one of its first call of proposals for "sustainable and affordable supply" of RUTF for the years 2008 to 2010[121]. The document solicits 20,000 metric tonnes, and reports that "RUTF is considered to be a key tool to achieve the Millennium Development Goals (MDGs)". Interestingly, the solicited forecasted procurement was limited to only twenty-two per cent of the countries where SAM was reported (data from UNICEF (2012)[41]), probably on the basis of priority ranking versus their SAM prevalence rates (see Table 5).

Ready-to-use therapeutic food spreads were used to treat and prevent other forms of malnutrition, for example wasting associated to HIV and/or TB infections. In this case, the results were conflicting. This type of wasting, an example of secondary malnutrition, is challenging to treat, because has "clinical characteristics and implications for treatment different from those better known in primary malnutrition". To what extent this is true is an increasing subject of study and debate [75]. For example, Ndekha *et al.* [116] compared the

weight gain in 491 underweight (BMI<18.5) HIV-positive adults, who received either RUTF or CSB. Survival did not differ in the two groups. However, the patients receiving fortified spread had a greater increase in BMI and fat-free body mass than those receiving corn-soy blend. Other authors report encouraging results in using RUF, but their studies did not have a control group[122–126]. For this reason, their evidence is less robust. Few other more convincing trials[125–128] and a recent review study[129] supported, evidence-based, the introduction of RUTF into HIV programmes for wasted adults. In 2011, treatment for the latter was reported to be available, at 23 per cent of the HIV treatment and care African programmes, supported by the President's Emergency Plan for AIDS Relief (PEPFAR)[130]. However, in adult HIV wasting, the issue related to survival remains not entirely understood.

Between 2007 and 2012, evidence on new versions of ready-to-use foods (RUF), and their effectiveness, was increasingly described in peer-reviewed publications. The new RUF are mostly in the form of paste and trialled against a variety of forms of undernutrition, in a range of age-groups, for supplementary and therapeutic purposes.

Recently, research and international humanitarian agencies have shifted their focus to prevention and treatment of children affected by MAM. In a three-arm RCT[131], moderately wasted Malawian children (WHZ >-3 and <-2) receiving a RUF based on soy and peanut, called ready-to-use supplementary food (RUSF), which is cheaper than RUTF, had a similar recovery rate to those receiving a fortified, more expensive RUSF. The latter was based on soy and milk. The children in either RUSF group were more likely to recover than those receiving porridge made from CSB. In 2008, in a UN conference on dietary management of MAM, Golden proposed nutrient requirements to rehabilitate children from this form of malnutrition, and published them the following year on the UN Food and Nutrition Bulletin[28].

In the same years, in Ghana, a placebo-RCT[132] tested the "hypothesis that multiple micronutrients added to home-prepared complementary foods would increase growth and that the effect would be greatest in the presence of added energy from fat". The three complementary foods were a micronutrient powder (brand: Sprinkles), a crushable micronutrient tablet (Nutritabs), or a micronutrient fortified RUSF spread (Nutributter). All the interventions showed positive effects on the children's development milestones,

however, only the RUF improved their growth velocity (data about fatality rate were not included).

In summary, in recent years the management of undernutrition began to rely on a range of industrial products. However, in spite of this proliferation, their classification, their design and the process of validation prior to their clinical trialling is not yet sufficiently explored and described.

1.2.2 Current classification

In spite of their increasing importance, RUF classification is insufficiently developed. Referring to RUF, USAID suggests that "the most significant change in food aid during the 21st century has been the arrival of a new family of products in the form of lipid-based spreads"[54]. WFP also argues that "the development of RUF have revolutionized the treatment of severe acute malnutrition, and catalyzed the development of other food-based commodities for treating and preventing less severe as well as other forms of undernutrition"[133]. In spite of their success, a general classification, internationally recognized, was not found. This observation can be extended also to the other food aid products. The Codex Alimentarius is the FAO/WHO "global reference point for consumers, food producers and processors, national food control agencies and the international food trade"[134]. Its web page (accessed on 28/02/2012; http://www.codexalimentarius.net) does not provide a classification of any product to manage undernutrition.

Although not internationally accepted, some definitions were proposed for lipid-based, paste-alike, ready-to-use foods. The following sections first report their definitions in the available literature, describing their nutrient contents, their processing, their safety aspects, and their supply chain. The last section explores important new areas of research.

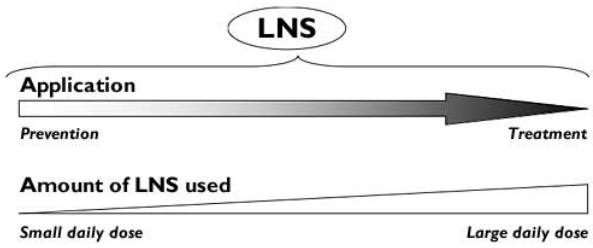
1.3 Ready-to-use foods for the management of undernutrition

1.3.1 Nomenclature

1.3.1.1 Ready-to-use, general term and the similarities with functional foods

RUF is a general term. Therefore, researchers from the iLiNS Project[135] suggested the term lipid-base nutrient supplement (LNS), should be defined as "a family of products designed to deliver nutrients to vulnerable people". Lipid-based supplements provide "a range of vitamins and minerals, but unlike most other multiple micronutrient supplements", because energy, protein, and essential fatty acids are also included (see Figure 9). These "formulations and doses can be tailored to meet the nutrient needs of specific groups and to fit in particular programmatic contexts".

Figure 9 - Relation between Application and Amount of LNS used.



Source: iLiNS Project [135].

However the term LNS can be misleading in some specific cases. For instance, when used for therapeutic nutrition interventions, RUTF is not a supplement, because it is used for exclusive feeding until recovery. For this reason, the form RUF will be preferred and maintained in the following sections. Furthermore, some RUF are not lipid-based such as Afya, a compressed food bar[136].

RUF for the management of undernutrition could be considered a specific type of functional food. The European Commission and the International Life Science Institute define functional food when:

> *"...(the food is) satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease.*

"…Functional foods must remain foods.

"…They are not pills or capsules, but part of a normal food pattern."[137].

Table 6 reports examples of functional foods, and whose global market is estimated to at least 33 billion USD per year[138].

Table 6 – Endorsed types of functional foods

Type of functional food	Definition	Example
Fortified product	A food fortified with additional nutrients	Fruit juices fortified with vitamin C
Enriched product	A food with added new nutrients or components not normally found in a particular food	Margarine with plant sterol ester, probiotics, probiotics
Altered products	A food from which a deleterious component has been removed, reduced or replaced with another substance with beneficial effects	Fibres as fat releasers in meat or ice cream products
Enhanced commodities	A food in which one of the components has been naturally enhanced through special growing conditions, new feed composition, genetic manipulation, or otherwise	Eggs with increased omega 3 content achieved by altered chicken feed

Source: Istevan *et al.* (2008)[139]

RUF could also be considered close to a functional food for other reasons. Sub-types of functional foods also include "spreads"[139]. However, this endorsed category currently consists of cholesterol-lowering products, "containing phytostanol esters which are supposed to lower cholesterol level"[139]. The spreads are currently commercialized in the form of margarines, milk, cheese, cream, and eggs[139,140]. For this reason, despite the existing similarities, the endorsement of lipid pastes for these purposes currently limit the application of the "functional food" definition to RUF spreads.

1.3.1.2 Ready-to-use therapeutic foods

In therapeutic feeding programmes for individuals with uncomplicated SAM, the term RUTF is widely used. In 2009, UNICEF suggested that RUTF are "portable, shelf-stable, single serving foods that are used in a prescribed manner to treat children with severe acute malnutrition"[119]. Among the most common RUTF brand names is Plumpy'Nut, produced by Nutriset (http://www.nutriset.fr) in France initially, and currently in ten other countries in Africa, Asia and America, including the US (Figure 10). Nutriset owns the patent on RUTF.

Figure 10 - Map and logos of the RUF manufacturers collaborating with Nutriset.

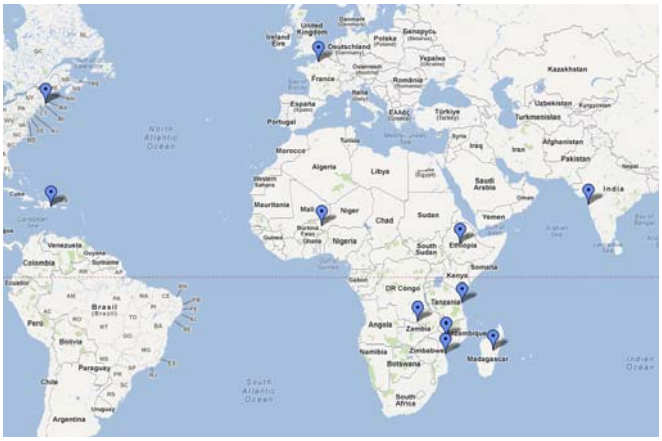


Table 7 - UNICEF-approved global RUTF suppliers

Global supplier	Product Name
1. Nutriset (France)	Plumpy Nut®
2. Vitaset (Dominican Republic)	Plumpy Nut®
3. Diva Nutritional Products (South Africa)	Generic name***
4. Insta EPZ (Kenya)	Generic name
5. Challenge Dairy (United States)*	Generic name
6. Tabatchnick Fine Foods (United States)	Nutty Butta
7. Compact (India)	EeZee Paste™
8. Compact (Norway)	EeZee Paste™
9. Edesia (United States)	Plumpy Nut®
10. Nutrivita (India)	Plumpy Nut®
11. JB/Tanjaka Foods (Madagascar)**	Plumpy Nut®
12. Mana Nutritive Aid Products (United States)	Generic name

**Dairy-based, not peanut-based, RUTF.*
***The first company located in programmatic country capable of exporting RUTF*
****Supplier agreed to remove branded name Imunut from the labels*

Source: Komrska[94].

Among other large manufacturers, Valid Nutrition (www.validnutrition.org), has two relatively large production sites located in Malawi and Ethiopia (personal communication; Steve Collins, 23rd March 2012). Compact, a Norwegian company

(http://www.compactforlife.com) also produces a RUTF, whose brand name is "eeZeePaste". Their manufacturing sites include Norway, Denmark but also Kenya, Dubai, India, and Malaysia. Other manufacturers from other countries are listed in Table 7, published in 2012.

Another example of RUTF is BP-100, produced by Compact, and more similar to a "compressed biscuit" than a paste. The World Bank argues that its "technology is more difficult to re-produce in developing countries"[40]. A similar consideration is also supported by other authors[141], and the available literature does not report the availability of this processing technique in any developing countries. However, in the food technology literature, no reference was found to confirm the World Bank statement.

This product also generated considerations of a different nature. In 2008, WFP was concerned with "the difficulty for the consumers to distinguish between nutritious and non-nutritious biscuits, and the possible promotion of a habit of biscuit consumption which may in fact lead to consumption of non-nutritious, high-sugar, biscuits"[142]. Because of these reported reasons, BP-100 will be not considered in the following sections of this thesis.

The main ingredients of the RUTF, trialled in the RCT described in other sections of this thesis, are peanut butter, milk powder, oil, sugar and the micronutrient premix.

1.3.1.3 Ready-to-use supplementary foods

A new category of product called ready-to-use supplementary foods (RUSF) are similar to RUTF in terms of appearance, but their formulation "addresses micronutrient deficiencies" in MAM. In 2009, UNICEF suggested that RUSF are "portable and shelf-stable products that meet the supplementary nutrient needs of those who are not severely malnourished"[119] and that "growing demand for RUSF products might decrease global demand for RUTF"[119]. The currently tested formulations[104,131,143,144] include ingredients such as soy, whey, lentils, rice together with oil, sugar and the micronutrient premix. Plumpy'Sup and Plumpy'doz are two of the RUSF commercialized by Nutriset[145].

1.3.1.4 Ready-to-use complementary foods

In 2012, Owino *et al.* [146] defined a ready-to-use complementary food (RUCF) as a paste "formulated to provide the recommended daily allowance of all micronutrients for 6 to 12 months old infants each day". In a first trial in Ghana[132], Nutributter, one brand from

Nutriset, provided significantly less daily energy than RUTF but a full complement of micronutrients in a similar group of children. The study showed that RUSF can prevent child stunting and support their normal motor development. Another study reduced iron deficiency in infants, using the same product[147].

In Malawi, similar products were tested in three other studies. In a RCT[148], a peanut/soy based fortified spread was associated with higher weight gain in infants, when compared with its control, a porridge fortified with fish powder. Another study[149] randomized infants to receive a year-long dietary supplementation with ready-to-use fortified spread or a traditional micronutrient-fortified maize-soy flour. The results did not show a significantly larger effect than the control on mean weight gain. However, incidence of severe stunting was tested in a followup study[150] with a double dose. In this case, the study showed that a twelve-month-long complementary feeding with 50 g/d of the same supplement was likely to have a positive and sustained impact.

QBmix and Plumpy'soy are other forms of RUCF, at least according to one of the leading manufacturers' perspective. From its website[3], Nutriset define them suitable for "prevention of nutritional deficiencies". QBmix is currently trialled in few studies, whereas Plumpy'soy used in pregnant women resulted in higher birth length than did a prenatal, multiple micronutrient, tablet-based supplementation[151].

In the literature, a number of acronyms and names were found for RUF products. The following section fixes the nomenclature used in this thesis.

1.3.1.5 Proposed nomenclature

As reported above, "ready-to-use" food is a generic term, and its sub-types can be many. The main subsets, previously described by Kerac[152] in 2010, include:

- RUTF = ready-to-use THERAPEUTIC food – for SAM in both children and adults
- RUSF = ready-to-use SUPPLEMENTARY food – for MAM in both children and adults
- RUCF = ready-to-use COMPLEMENTARY food – for general use as a complementary food or for preventing malnutrition in infants and young

[3] http://www.nutriset.fr/.

children

Since then, the rapid proliferation of RUF has increased. Their ingredients, their nutrient specifications, and target age-groups, differ within the same RUF sub-types. Therefore, the following nomenclature may be better at distinguishing RUF sub-categories.

XXX-RU**Y**F-**ZZ**

The "Y" letter designates therapeutic (T), supplementary (S) or complementary (C), whereas "X" and "Z" can include further pieces of information:

- The ingredients of the RUF (letter "X")

  Not all the ingredients need to be mentioned. Oil and sugar are common to most RUF. Therefore, only the other food ingredients are to be indicated. The first ingredient reported is the one in higher weight per centage, whereas the others follow a decreasing order.

- Other information – (letter "Z")

  Acronyms suggest the life-stage and/or other aspects.

For instance the acronym for a theoretical RUF, whose formulation addresses moderate malnutrition in children under five years and living with HIV, and whose ingredients include soy, lentils, rice, oil, sugar and a micronutrient premix, may be termed "SLR-RUSF-U5H". This is more clearly explained, as follows:

S = soy
L = lentil
R = rice
RUSF = *ready-to-use* supplementary *food*
U5 = under five years of age
H = HIV

1.3.2 General description

1.3.2.1 Nutritional aspects

Table 8 - Nutrition composition of RUTF

Moisture content	2.5% maximum
Energy	520–550 Kcal/100 g
Proteins	10%–12% total energy
Lipids	45%–60% total energy
Sodium	290 mg/100 g maximum
Potassium	1,100–1,400 mg/100 g
Calcium	300–600 mg/100 g
Phosphorus (excluding phytate)	300–600 mg/100 g
Magnesium	80–140 mg/100 g
Iron	10–14 mg/100 g
Zinc	11–14 mg/100 g
Copper	1.4–1.8 mg/100 g
Selenium	20–40 µg
Iodine	70–140 µg/100 g
Vitamin A	0.8–1.1 mg/100 g
Vitamin D	15–20 µg/100 g
Vitamin E	20 mg/100 g minimum
Vitamin K	15–30 µg/100 g
Vitamin B1	0.5 mg/100 g minimum
Vitamin B2	1.6 mg/100 g minimum
Vitamin C	50 mg/100 g minimum
Vitamin B6	0.6 mg/100 g minimum
Vitamin B12	1.6 µg/100 g minimum
Folic acid	200 µg/100 g minimum
Niacin	5 mg/100 g minimum
Pantothenic acid	3 mg/100 g minimum
Biotin	60 µg/100 g minimum
n-6 fatty acids	3%–10% of total energy
n-3 fatty acids	0.3%–2.5% of total energy

Source: UN Joint Statement (2007) [55]

RUF must contain most of the "40 nutrients essential for health"[28]. Nutrient standards have been proposed by the UN for RUTF[55]. These specify energy in RUTF 500-1,000 Kcal/d, total lipids (45-60 per cent), protein contents (10-12 per cent per cent of their contribution to the total energy), and essential fatty acids such as omega-6 (3 to 10 per cent of total energy) and omega-3 (0.3 to 2.5 per cent of total energy). In RUSF the omega n-6/n-3 ratio should be below 15 and preferably between 5 and 9[153]. The standards for RUTF are reported in Table 8. In 2012, WHO proposed the nutrient composition of supplementary foods for use in the management of moderate acute malnutrition in children[154], assuming that the supplementary food covers 70% of their energy intake .

In 2007, a UN Joint Statement document specified 23 micronutrients RUTF standards of both type I and II, in the form of range, or of minimum amount. In 2009, Golden[28] argued that an improved way to describe the standards for RUSF consists of nutrient/energy densities, expressed as unit of each nutrient in 1,000 kcal of the product.

Protein quality in RUF is important. This parameter is recommended by WHO to be measured using the protein digestibility-corrected amino acid score (PDCAAS)[155]. In RUTF for children under five, "at least half of the proteins contained in the foods should come from milk products" according to the UN Joint Statement (2007). Based on simple

calculations, this statement corresponds to a PDCAAS of at least 100 per cent[156]. More recently, the UN have endorsed a new, but more complex method to evaluate protein quality content in foods[157].

Figure 11 – Examples of equipment for spray drying for milk and whey powders (a), and of extrusion of cereals and pulses blends (b).

(a) (b)

Source: web sites of MilkPowderTech[484] and ACF Mechanical Equipment[485].

1.3.2.2 Ingredients, processing, packaging and safety

The iLiNS project web site (http://www.ilins.org/; accessed 05/03/2012) suggests that RUF formulations "can include a variety of ingredients, but typically contain vegetable fat, peanut/groundnut paste, milk powder and sugar." This was true for the first clinical trial, in 2003, undertaken by Diop *et al.* [71] confirming the same efficacy in weight gain for both RUTF and F100 formula milk in children with SAM. Since then, the ingredients were replaced by others. iLiNS reports that "alternative recipes and formulations are currently being explored in efforts to develop affordable and culturally acceptable products for a range of settings. Other ingredients have included whey, soy protein isolate, and sesame, cashew, and chickpea paste, among others".

Figure 12 - Packaging of RUF: sachet and cup.

Source: Nutriset [145]

Figure 13 – Child self-administering RUF.

Source: Valid Nutrition.

Manary reported that RUF "production sufficient to meet the needs of several thousand children can be achieved with a dedicated manufacturing facility

using technology appropriate for use in the developing world"[158]. The processing technology and production sequence changes according to the ingredient choice. However, spray-drying, a sophisticated industrial process, is needed to transform milk or whey into powders, while extrusion, common also in most developing countries, is used to pre-cook blends of cereals and pulses, gelatinizing their starch and partially destroying antinutritional factors[159] – see Figure 11.

Most RUF are provided to the beneficiaries in sachets or cups. The content of the sachet can be squeezed directly into the child's mouth, reducing the risk of environmental contamination – see Figure 13. In case of the cup, the content must be scooped, and the risk of contamination is higher. The form of packaging is crucial for the effectiveness and the safety of the product. Koethe *et al.* [129] reports that "RUTFs, like other highly nutrient-dense spreads, can be stored for long periods, do not require refrigeration, and can be individually packaged and used effectively, in areas where hygiene conditions are not optimal".

Table 9 - Maximum toxin levels allowed in RUTF

Aflatoxin level	10 ppb maximum
Microorganism content	10,000/g maximum
Coliform test	negative in 1 g
Clostridium perfringens	negative in 1 g
Yeast	maximum 10 in 1 g
Moulds	maximum 50 in 1 g
Pathogenic Staphylococci	negative in 1 g
Salmonella	negative in 125 g
Listeria	negative in 25 g

Source: UN Joint Statement (2007) [55]

Safety standards are specified by the UN 2007 Joint statement[55] and include international maximum levels for aflatoxins and microorganisms such as coliforms, clostridium, yeasts, moulds, pathogenic staphylococci, salmonella and listeria – see Table 9Table 9. RUTF should comply with the Recommended International Code of Hygienic Practice for Foods for Infants and Children of the Codex Alimentarius Standard CAC/RCP 21-1979 (available at http://goo.gl/jp7Yg). While all added mineral salts and vitamins should be on the Advisory List of Mineral Salts and Vitamin Compounds for Use in Foods for Infants and Children of the Codex Alimentarius Standard CAC/GL 10-1979 (available at http://goo.gl/5RDsE).

1.3.3 Institutions and organizations with interest in ready-to-use foods

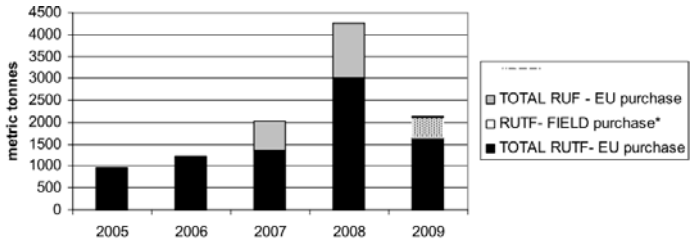
RUF are a fundamental element in feeding programmes supported by UN agencies, non governmental organizations (NGOs) and by an increasing number of national governments.

UN agencies are large purchasers of RUF. Since 2007, the mandate of UNICEF provides

advocacy, supply and logistic support to other governmental and non governmental institutions and organizations involved in therapeutic feeding for uncomplicated children in community settings[160]. UNICEF is "the leading global procurer of RUTF"[119]. UNICEF Country Offices identify the needs and obtain funding for RUTF. A purchase order is processed through the UNICEF Supply Division and released to the manufacturers, initiating the production and transportation around the world[119].

UNICEF is not the only UN agency involved in RUF procurement and delivery. Section 1.2.1.4 of this thesis reported the exponential increase of UNICEF demand for RUTF since 2007. Similarly, WFP, another UN agency, is constantly augmenting its procurement of RUSF. In 2012, the WFP Executive Board released the Nutrition Policy Item number 5[3], which puts the three following priorities at the very top of its agenda: (i) treating moderate acute malnutrition (wasting); (ii) preventing acute malnutrition (wasting); (iii) preventing chronic malnutrition (stunting). Talking about the way to achieve these goals, the policy paper reports that WFP "in recent years, has scaled up the use of lipid-based, ready-to-use foods, such as peanut and chickpea-based pastes". The policy paper reports that "in the absence of specially developed foods for adults with undernutrition related to HIV or tuberculosis, ready-to-use products are also increasingly used for these groups". WFP reaches more than 90 million beneficiaries of many ages every year[3].

Figure 14 - Trend of RUTF and RUF deliveries (MSF)



Source: MSF Nutrition Working Group – Report 2009 [4]

In many feeding interventions, NGO are partnering with UNICEF, WFP and sometime with national governments. In these partnerships, NGO receive and deliver the RUF through their own feeding programmes. Nevertheless, some NGO often procure directly their volumes of RUF spreads[119]. From 2004 to 2008, MSF, one large NGO, purchased 30 per cent of the total amount of RUTF on the global market (see Figure 15), and in 2009 distributed 20 per cent of the entire RUTF world production[4] treating 208,922 people with SAM. Other NGO procuring RUF are Action Against Hunger, and Concern World Wide, but no data were found for these organizations.

Figure 15 - Logos of the academic institutions, NGO and private enterprises involved in the iLiNS project.

Source: iLiNS Project[135].

The President's Emergency Plan for AIDS Relief provides nutritional support services in HIV care in sub-Saharan African countries. In 2011, Anema *et al.* [130] found that in a total of 336 HIV care and treatment sites, serving 467,175 patients, 31 per cent treated SAM using some sort of RUTF.

Figure 15 shows the logos of the few African, American and European academic institutions and one manufacturer interested in the development and improvement of RUF spreads. International Lipid-Based Nutrient Supplements (iLiNS) Project is a "research collaboration that grew out of a shared commitment to accelerate progress in preventing malnutrition". This academic-private sector partnership, based at University of California / Davis, includes the universities of Tampere (Finland), Ghana and Malawi, the Research Institute of Burkina Faso, the NGO Helen Keller International, Project Peanut Butter, and the enterprise Nutriset.

Another university in Europe focuses on crucial aspects directly related to RUF production. The Irish University of Cork has recently engaged on a research looking at the impact on livelihood and market opportunities for Malawian smallholder farmers supplying plant-based ingredients for a local RUF factory[161]. The project is undertaken in collaboration with Valid Nutrition.

Some organizations and manufacturers sought ways to produce without conflicting with the patent restrictions. In 2007, Nutriset and Valid Nutrition signed a "Licence Agreement"[162]. This document enabled "Valid Nutrition to independently manufacture peanut based RUF covered by the Nutriset patent in developing countries and to market these products under the Valid Nutrition brand name"[162]. However, further criticism was targeted at the existence of the patent. In 2009, MSF wrote an open letter "calling for the establishment of a more flexible licensing policy"[163]. Nutriset responded formally, and initiated a new market strategy. Today, on reaching agreement with Nutriset, companies and NGOs are allowed to make the patented pastes in African countries with the Nutriset logo on the product labels

and without paying any license fees[164]. However, the debate has continued up to present and in 2010, two non-profit American organizations sued the French company in order to remove the patent protection[165]. The result of this legal action is currently unknown.

A report from the Duke University in collaboration with UNICEF[119] describes how, in low-resources countries, Ministries of Health (MoH) "work with national or international NGO partners, and the UNICEF Country Officer, to release RUTF for distribution to the districts, where the District Nutrition Officer and/or NGO partners store RUTF until it can be used". These MoH have showed a wide range of responses towards the introduction of RUF products. In some cases they endorsed directly the latter into their policies and nutritional protocols, whereas in others, they took more evidence-based approaches. The two extreme cases may be represented by the recent events in Kenya and India, two countries whose prevalence of mild to severe wasting were estimated to be respectively of 7 (2008 and 2009) and 20 per cent (2005 and 2006)[41].

1.3.3.1 The Kenyan case

Kenya represents a successful case of integration of RUF into national protocols endorsed by the MoH. Since RUTF was endorsed by the UN in 2007, the demand for RUTF by humanitarian organizations in East Africa has far exceeded the available supply. In 2012, USAID reported[54] that "too few regional businesses are willing to tackle the challenges that RUTF manufacturing presents". Insta Products is one of them. This Kenyan processing factory located in the outskirts of Nairobi since 2009, supplies an average of 4,500 metric tons of RUTF per year across the region, reaching vulnerable populations in Ethiopia, Somalia and Sudan (personal communication; Stuart Allison, Insta Manager; 2011).

In Kenya, RUTF is currently "prescribed" to HIV wasted patients. With 6.7 per cent of HIV national prevalence, 1,200,000 infected Kenyans and 50 per cent of the population are living in food insecurity (data from 2005)[166]. The Government soon became aware of the benefits that, via Insta, a public-private collaboration could provide to the health of its citizens. Since 2010, with the support of USAID, the local MoH has included RUF in the HIV-related services package, for in- and out-patient hospital care. One of the pillars of the programme is a private-public partnership that includes capacity building within Kenya's Ministries such as Medical Services, Public Health and Sanitation, as well as with grass-root organizations[167]. In the protocol endorsed by the government, RUTF is "prescribed" in combination with normal food rations for household consumption[167]. Currently, the

programme includes 155 primary health sites, which facilitate support to 261 satellite health facilities. By June 2010, the HIV nutrition program reached a total of 171,281 clients, 46 per cent of which were malnourished adults[167] (no further data about reduction of fatality rate or recovery was provided in this document).

1.3.3.2 The Indian case

In India, in 2008, RUTF procurement was at the centre of a debate between the local MoH and UNICEF. This country represents an important case study because the SAM case load, in this country, is extremely large. More than eight hundred thousands under-five Indian children suffer from severe acute malnutrition[168]. For decades Indian hospitals have treated SAM with local foods, similarly to what reported in Africa before the arrival of F100 and RUTF[105].

In 2008, the government of India started a dispute with UNICEF over RUTF introduction in the country[169]. UNICEF imported a large quantity of RUTF to treat children with SAM in two Indian states, apparently without the authorization from the local authorities. Therefore, the national government stated that these supplies were to be sent out of the country. The collaboration between UNICEF and the Government became difficult, as reported by the international press. A peer-reviewed article[170] from the Indian "Working Group for Children Under Six" argues that "it is hard to explain why it has been permitted for a somewhat alien product to be introduced at such large scale".

This debate was only started in two Indian states, but soon it became a concern for the entire country. In 2009, the MoH organized a "National Consensus Workshop on Management of Children with SAM through Medical Nutrition Therapy". On this occasion, representatives from the Indian MoH, NGO and research community had the chance to discuss the use of RUTF to treat SAM in uncomplicated children at community level. Valid International and MSF supported my participation at the conference.

Less than a year later, the journal Indian Paediatrics (volume 47, number 8) published an issue with nine original papers written mostly by Indian authors. Based on the available evidence, the papers supported the endorsement of RUTF, and urged the improvement of the existing guidelines. Their evidence-based conclusions are expected to contribute, in the long run, helping India to catch up with the rest of the countries treating their severely malnourished children with RUTF.

Some of these articles critically looked at the African experience. Three papers included systematic and narrative reviews of the efficacy, the safety and the coverage of RUTF-based interventions in Africa[9,62,101]. The same journal issue looked also at what was done in India. Two studies[171,172] evaluated the feasibility and the outcome of home- and hospital-based rehabilitation of severely malnourished children without using RUTF or F100, but using local Indian dietary prescriptions. Both studies showed that the recovery rate in the children was suboptimal. A third study, describing a randomized controlled trial, assessed the effectiveness of a locally made therapeutic spread in decreasing mild to moderate malnutrition. The authors report that "the RUTF was prepared at a local bakery and packed into polythene bags (250 g per bag), heat-sealed and distributed to the pre-schools. The RUTF was produced by mixing together ground roasted peanut butter, milk powder, sugar and gingili oil". The latter, based on *sesamum indicum*, is commonly used to soften hair and skin in India. Therefore, it can be argued that its use was culturally acceptable. In the same trial, the control consisted of the current standard of care, consisting of "teaching caregivers how to make a fortified cereal-milk supplement", similar to a porridge. The author concluded that "community-based treatment showed weight gain in both groups, the gain being higher with RUTF".

The same journal issue described the local production of fortified lipid-based spreads. One study reported that "production of RUTF is a simple process", and that "all the ingredients and equipment for RUTF are widely available" locally. The authors explore three production models already tested in India: (i) dairy cooperatives and private manufacturers able to produce large quantities to meet regional requirements, (ii) small and niche food manufacturers producing smaller volumes, but with a larger presence in most parts of India; and (iii) "hand made" RUTF manufactured by "village industries" for immediate local consumption. The publication concluded suggesting that "it is time public health/ medical communities and civil society come together to make effective community management of SAM an immediate reality".

A paper titling "Management of Children with Severe Acute Malnutrition: A National Priority"[173] closed the Journal issue. One of its sections reports that in India "there is unprecedented political and bureaucratic will to address the national embarrassment of SAM" and that "the national funding agencies and Indian scientists also perceive the need

for prioritising this area for research". The conclusive sentence warns that "arguments against product based nutritional therapy in community settings should not obstruct urgent evidence creation to feed national policy".

1.3.4 Current research areas

The potential of RUF products has just recently started to be fully recognized, opening wide areas of research. WFP recently confirmed that RUF have a role to play[3], being not only in high demand, but also in an increasingly variety of forms[54], addressing nutritional issues in new target groups. This seems to be confirmed by the number and the pace of evidence published in the last few years. Only a sample is reported here.

In 2009, Chaparro and Dewey[174] suggest that, in large general food distributions, RUF spreads may have more potential to reach children under two and pregnant and lactating mothers, than other food commodities, however, more evidence is needed. In 2012, in a factorial randomized trial, RUF spread was showed to mitigate weight loss among HIV-infected women during exclusive breastfeeding[175]. Some authors concluded that this is a "rapidly changing area of research"[54], and reporting that currently "numerous studies are ongoing"[54].

Despite research in RUF is ongoing, some areas may not be receiving adequate attention. The following section describes important problems and knowledge gaps that I have identified and will be tackled in the rest of this thesis.

1.4 The problems and the knowledge gaps

Some aspects of therapeutic, supplementary and complementary feeding with RUF spreads require more evidence-based understanding. Some authors raised this specific point when looking closer at the available knowledge about RUTF and SAM management. However, the same apply to most of the other RUF spreads. For instance, the current RUTF formulation is based on results from a limited number of studies, in a few settings, showing rapid weight gain. The latter may not be ideal when leading to a rapid increase in fat rather than lean body mass, and negative, long term, health consequences. Moreover, in other settings, with different underlying nutrient deficiencies and infectious disease profiles, similar weight gains would perhaps occur with nutrient levels different from those in use[95,176–178]. Therefore, exploring these hypotheses is important. However, testing improved RUF prototype formulations is costly.

Improving each preliminary phase of their design, before trialling their clinical effectiveness in expensive studies, is therefore crucial.

1.4.1 How should improved RUF products be designed?

The peanut-based of Ready-to-Use Therapeutic Food was not a formulation optimized, whose target goal was the lower cost. Instead its original design aimed at being as little different as possible from the existing F100 product, which was known to be efficacious in rehabilitating children from severe acute malnutrition.

Therefore, a validated method to design and trial novel optimized RUF is currently not available. This was officially recognised only in 2008, during the conference which approved the use of RUSF spread to prevent and/or treat MAM[28,153]. UN, NGO and academic bodies expressed the need for an evidence-based method to test and validate novel improved RUF[179]. This is a strategic aspect, because it potentially affects future developments in the treatment of many forms of undernutrition, in other life stages.

One of the conference documents suggested, as a followup activity, “to design a complete framework to test a new product”. However, at present, there is no internationally endorsed protocol to design products of this kind.

1.4.2 How can novel RUF acceptability and safety be tested, prior to trialling their effectiveness?

Testing the acceptability and the safety of improved RUF spreads can be challenging. That may be described by a few examples. The formulation of the RUTF currently used in most therapeutic feeding programmes includes milk powder and peanut butter. These two ingredients seemed to be among the causes of a low level of acceptability among beneficiaries in Cambodia, as reported by MSF[180]. A qualitative socio-anthropological investigation, conducted by Boudier, from the French Institute of Research for Development (IRD) explored this aspect[181]. A traditionally accepted ingredient (fish sauce) was introduced into the formulation, and its preference assessed in a trial with a simple design [180]. The results were not in favour of the novel formulation. Safety was not included among the parameters.

In India, for similar reasons, another formulation was designed and more successfully tested for its acceptability. Thirty-one wasted children were offered pre-set amounts of RUTF or its control, a local porridge, in unlimited amounts for two days. Energy intake and acceptability were the primary outcomes of this trial. Only one child was excluded after becoming sick during the study. After a statistical analysis of the data, the conclusions were that the RUTF and its control "were both well accepted". At the time of this thesis, a literature review did not highlight any effectiveness trial based on the described product. However, in the acceptability trial, it could be argued that the limited time of exposure to the spread may have not been sufficient to highlight potential risks of side effects.

In Malawi, similar conclusions from an acceptability study had a negative impact on the subsequent RCT. Fellows (personal communication; 2008) reports that an initial pilot study, with no control for comparison, that tested the preference for an improved RUTF in wasted children, showed high acceptability, among children and caretakers, after one day of testing. Chickpeas and sesame were among the ingredients. The RCT was therefore initiated. However, the randomized delivery of the improved RUTF had to be soon interrupted. The reason was that, after few days, the care givers had reported, in their children, a stomach pain consistently associated with the RUTF consumption. The trial was, therefore, never concluded.

However, a few important lessons were learnt. Changing ingredients may result in a

negative impact on the health and, potentially, the survival of vulnerable undernourished people. Moreover, trials with a short duration, and/or weak design, may fail to identify potential risks of low acceptability and safety. Therefore, it was agreed that any sort of deviation from tested RUF formulations should be carefully based on sound evidence, derived from robust randomized controlled trials (RCT)[182]. However, at present, there is little agreement about how to adequately assess the acceptability and the safety in products of this type.

1.4.3 What is the adherence to paediatric RUF formulations when used for older people?

A paediatric RUF is currently used in adults. In 2007, the UN officially approved the use of RUTF for the treatment of acute malnutrition in children under five years of age [55]. The same paediatric formulation is currently supplied to large HIV programmes aiming at the nutritional rehabilitation of wasted adults. However, as reported in section 1.2.1.5, this formulation is costly, and its choice in this life-stage group only partially supported by conflicting evidence[116,127]. These controversies were recommended to be urgently better understood[129]. Understanding patients' adherence to RUTF may shed some light.

Looking at how adult patients comply with a prescription based on the paediatric RUTF formulation seems crucial, but the current data are little. Furthermore, the method designed to carry this research may suggest lessons to improve the RUF spread and/or its delivering intervention.

1.4.4 How can the cost of RUF be minimized?

Ways to reduce RUF costs need to be further explored and improved. According to UNICEF[119], sixty-eight per cent of Plumpy'Nut final overall price, excluding manufacturing and transport costs, consists of food ingredients. In Kenya, in March 2008, one kilogram of Plumpy'Nut costs approximately 5.00 USD (personal communication: Malik Allouna, MSF/France, Kenya mission). This suggests that the indicative price for the food ingredients component was 3.4 USD/kg.

In RUF, some ingredients are more expensive than others. Milk powder, when present, represents ~50 per cent of the final cost, and cheaper food ingredients are in demand to replace it. In 2011, whey powder was recommended by some large donors[54], in spite of the fact that experts voiced the need to test its safety first[183,184]. However, whey is only 20 to 40

per cent cheaper than milk, is not available anywhere, may be culturally unacceptable in countries where unknown, and requires sophisticated technology. Therefore, solutions at lower cost should be urgently sought.

Lower transport and reduction of importation costs are likely to result in a price advantage for locally produced RUTF. The regional agriculture economy may benefit due to local purchase of the ingredients, increasing national self-reliance on local food crops. Based on these considerations, frequently found in the international debate about RUF use, it would be very advantageous if locally available and cheaper commodities could replace expensive imported food ingredients in future formulations. However, replacing costly ingredients, while still meeting each of the nutritional standards described at page 67 and avoiding an extended trial-and-error approach is likely to be challenging.

Therefore, a crucial knowledge gap is how to develop a method for designing the cheapest formulation of a RUF that fulfils pre-defined nutrients requirements, using region-specific foods that are culturally acceptable, and that can be processed with locally available technologies.

1.4.5 How can micronutrients specifications in novel RUF be determined, when requirements are unknown?

In some forms of malnutrition of global public concern, evidence may be often too little or too weak to determine improved nutrient requirements. Therefore, the specifications for RUF cannot be determined. An example is provided by wasting associated with HIV. The current RUTF formulation showed relatively satisfactory survival rates in children affected by HIV and/or TB[43,185]. However the same is not true in adults[116], and a recent systematic review study urges further research "to test high-dose multiple micronutrient supplements" which "may be appropriate only for short-term nutritional rehabilitation in underweight and malnourished adults with HIV"[75].

No evidence-based method to determine micronutrient specifications for RUF, when nutrient recommendations are unknown, is currently available. However, there is an urgent demand for this method, and its applications.

2 Rationale, aim, study plan, objectives and research questions

2.1 Rationale

This area of research is strategically important for global nutrition and health. The thesis explores the development of methods to fill the knowledge gaps described above. These methods will be incorporated into an overall framework for the design and preliminary testing of novel RUF products that I will develop.

With these reasons in mind, I conceived the following general aim and objectives. They are summarized here and explored in detail in the next chapters of this thesis.

2.2 General aim

To develop a series of methods and an overall framework for the design and preliminary testing of lower cost, lipid-based ready-to-use foods, for the prevention or treatment of undernutrition.

2.3 Study plan: the case-study, the sub-studies, and their objectives

The study plan was composed by four separate sub-studies, each with one specific objective and method. A case-study helped to assess the methods, when applied to design an improved RUF.

2.3.1 The case-study

The case-study was selected purposively. Its application aimed to highlight lessons to learn from the practice. The choice of the case-study took into account each of the described knowledge gaps and problems.

For this purpose,

> I selected the design of a low-cost, acceptable and safe RUTF, specific for wasted adults, living with HIV with (or without) active TB.

This case-study covers all the raised issues related to RUF design and testing. The prevalence of HIV wasting among adults is a public health concern, as described in section 1.1.2.1. In this group, the current paediatric formulation for RUTF does not seem to

increase survival, as reported in section 1.2.1.5. Therefore, a framework to design a novel formulation is urgently needed (issue number 1 described in section 1.4.1). The improved RUF should be acceptable and safe (issue number 2 in section 1.4.2). The section 1.4.3 describes how the design must be consumer-driven. Therefore, the product improvements must be based on the preferences and the suggestions expressed by the wasted adults currently or previously exposed to the most common product (issue number 3 in section 1.4.3). The novel formulation must be economically viable, therefore its cost should be as cheap as possible (issue number 4 in section 1.4.4), while still meeting its nutrients specifications. Little is currently known about the micronutrient recommendations for adults with HIV wasting, associated or not with TB. Therefore, in this specific group, the RUF micronutrient specifications represent an additional challenge (issue number 5, in section 1.4.5).

2.3.2 The sub-studies

Each problem or knowledge gap described in sections 1.4.1 to 1.4.5 guided the overall research aim. In accordance with the framework method, the general research purpose was broken-down into four sub-studies, which were applied to the selected case-study. Each sub-study had a specific aim, met a specific objective, and responded to an individual research question.

Sub-study 1 - Adherence and key barriers

Aim of the study:	Development of a method to understand the factors affecting usage of current formulations of RUF
Specific objective:	To investigate compliance with RUTF in a HIV/TB therapeutic nutrition programme in Kenya
Research questions:	(i) what is the adherence to a protocol, when using a specific RUTF (Plumpy'Nut), among malnourished adults living with HIV?
	(ii) what are the key barriers to their adherence?

Sub-study 2 – Formulation of improved ready-to-use foods

Aim:	Testing of a method for optimal design of novel RUF formulations
Specific objective:	To design a formulation that fulfils the international macro-nutrient requirements and food-related standards for the design of a cheaper RUF
Research question:	How can a linear programming based method be used to design the cheapest formulation of a RUF that fulfils pre-defined macronutrients requirements, and uses regionally-specific foods which are culturally acceptable and can be processed with locally available technologies?

Sub-study 3 - Acceptability and safety

Aim:	Development of a method for trialling the acceptability and safety of a novel RUF formulation
Specific objective:	To compare the acceptability and the safety of a novel RUF with the most commonly used product, using a randomized controlled clinical crossover trial with HIV/TB patients in Kenya
Research question:	What is the consumption, safety, and preference for a novel RUTF, in comparison to the current standard product used to manage HIV/TB wasting in adults?

Sub-study 4 - Designing micronutrient specifications when requirements are not available

Aim:	Development of a method for deriving recommended RUF micronutrient specifications for malnourished groups

Specific objective:	To design a method to derive micronutrient specifications in a RUTF for wasted adults living with HIV/TB, whose requirements are currently unknown.
Research question:	What are the micronutrient specifications for a RUTF to manage HIV/TB wasting in adults?

3 Understanding the challenges in current usage of ready-to-use foods: an investigation of adherence in a HIV/TB therapeutic nutrition programme in Kenya (sub-study 1)

3.1 Adherence

In the human history, the importance of therapeutic adherence was early recognized. In ancient Greece, Hippocrates was aware of the fact that patients pretended to have taken their medication[186]. At the end of the 1950s, three physiologists drew closer attention to the adherence phenomenon, studying the therapeutic effects of a tuberculostatic agent in out-patient settings[187]. Later, in 1975, David Sackett described adherence in depth, when low compliance was found responsible for unpredictable or disappointing responses to one treatment of hypertension[188]. The same author states that much still needs to be understood in this area of research.

According to Donovan, in 1995, "one of the most striking reasons for the lack of progress in compliance research is the absence of a crucial factor: the patient's perspective"[189]. The latter is the element which distinguishes *adherence* from *compliance*. According to the large variety of definitions available in the literature, compliance "is a word with negative connotations. It suggests yielding, complaisance and submission" [190]. The patient should not be perceived as "passive, acquiescent recipient of expert advice as opposed to an active collaborator in the treatment process"[191]. Therefore, based on this new perspective, WHO proposes the following definition of *adherence*[191]:

> *"The extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".*

Claxton *et al.* agrees with this definition, suggesting that adherence is "an essential component of a successful health outcome", and, most of all, is "largely in the domain of the patient"[192].

In a review of seventy-six studies, the same author concludes that the definitions of adherence are numerous and varying because of the many ways in which it was assessed and measured[193]. However, distinguishing degrees of adherence, such as *partial* or *total non-adherence*, may be challenging. For instance, when dose-taking and dose-timing measures are used, *partial non-adherence* can be defined as "taking less then the

prescribed amount of medication or taking the medication at inappropriate intervals" [193], whereas "*total non-adherence* can be defined as discontinuation of treatment"[193].

Currently, there is no agreement on cut-offs for partial- or non-adherence levels. However, based on a review of the available literature, Krueger *et al.* found that most authors considered non-adherence when the consumption of the doses prescribed was lower than 80 or 90 per cent, "while others considered any missed dose as evidence of non-adherence"[194]. Moreover, from the classification point of view, there is agreement that patient's non-adherence can be both "intentional or unintentional"[190].

In UK, the term *concordance* has been also used to define adherence or compliance. In 1998, the members of the Royal Pharmaceutical Society of Great Britain considered that the way of thinking about compliance was insufficient[195]. Therefore the current terminology was changed from compliance to *concordance*, "which means agreement and harmony". The concordance approach considers "the patient as a decision maker"[195], and her/his "professional empathy" with the medical staff[196] the cornerstone of the treatment success.

Because of its current large use in the found literature, in this chapter, despite its semantic limitations, *adherence* remains the preferred term.

3.1.1 The importance of adherence

In the literature, there is consensus that adherence to treatment is important, and its reasons are many. Adherence is a "key link between process and outcome in medical care"[190,197]."The responsibility for fulfilment of the prescribed regimen lies with the patient"[192], and the most carefully chosen and optimal medication cannot work, if the patient does not take it appropriately"[192]. This is consistent with the available evidences. For instance, a literature review[192] has confirmed the direct relationship between the number of daily doses, rate of adherence, and positive health outcomes. This was found also in complex treatment regimes where sophisticated electronic monitoring systems were in use[198].

It can, therefore, be argued that "non-adherence is detrimental", because it "wastes resources, and causes preventable morbidity and mortality, and the loss of healthcare dollars and productivity"[199]. However, authors recognize that systematically reviewing non-adherence in the available literature can be challenging, because the documented evidence

is little. This seems to be because researchers are aware that when measurements of adherence are considered, the interpretation of the results can become complex, while "studies with significant results could have a greater likelihood of publication"[199].

According to the available evidence, however, investing resources in improving adherence is expected to be cost-effective. Claxton *et al.* reports that "health care personnel expend many resources caring for patients who do not respond to initial treatment with a new drug"[192].

In low-income countries, absence of information about adherence to nutrition programmes hampers the evaluation of their effectiveness. For instance, the World Bank [40] reports that nutrition "interventions have been deferred … because data on compliance and delivery mechanisms are unclear". To support this statement the report uses the cases of zinc and calcium supplementation programmes in African and Asian countries[40].

Very similar considerations are applicable also to out-patient nutrition programmes, where lipid-based RUF spreads are used. In 2002, Collins *et al.* [200] voiced the importance of understanding "the role of community groups and mother-to-mother educational techniques" to improve adherence in community-based treatment of SAM. Almost ten years later, in 2011, similar recommendations are again found in the scientific literature. In a HIV care programme, in Uganda and Kenya, supported by MSF, Ahoua *et al.* [127] highly rank the "understanding of adherence" with RUTF-treatment to improve health outcomes, and to make the same intervention more cost-effective.

3.1.2 The determinants of adherence

The literature describes a large number of determinants of adherence to treatment. These include factors related to the environment in which the patient lives, the setting in which the treatment is supplied, and the counselling session, if any, that comes together with the regimen. This section first describes the determinants in general settings, and secondly focuses specifically on low-resources contexts, and in particular on nutrition programmes.

The environment of the patient is an important determinant for adherence because "patients live in a social environment. Social support involves the help that family members, friends, or caregivers provide to help patients adhere to their medication regimens"[194].

Therefore, it should not be surprising that "patients who believe they have social support demonstrate greater treatment adherence" [194]. Other review studies [193,201,202] confirm that "family cohesion and the stability of home life", together with patients' membership to one or more support groups appear to be additional predictors of adherence.

The clinical setting also influences the degree of adherence. For instance, in health service settings, Krueger *et al.* [194] found that "long waiting periods and a lack of continuity of care are more likely to lead to non-compliance".

However, counselling and the relationship between patient and health staff are among the strongest determinant of adherence. In a large review study, Vermeire *et al.* [190] report that the non-adherence is associated with the complexity of medical regimens, as much as poor communication, and patients' concerns, which the health staff were unable to solve. For this reason, it was concluded that adherence "seems to be related to the quality, duration and frequency of interaction" between the patient and health service provider [190].

Counselling is one of the most important forms of interaction between patient and health staff. In nutrition and medical interventions, "regular dietetic followup and detailed discussion of the disease by the physician have also been found to be associated with adherence" [193,203]. One study suggested some possible reasons. Correct application of counselling techniques may trigger a "patient's belief that a medication will work or is working"[194], enhancing the patient's "ability to endure the side effects" of the treatment, and maintaining "a positive attitude" [194]. Not surprisingly, in another review study, Hall *et al.* [193] found that adherence was not necessarily associated with "correct knowledge" in the patient group, but when the health staff had confidence in the treatment effectiveness [193]. The same author [193] also suggests that health staff's "descriptive accounts and explanations of the illness" and the treatment can influence both the attitude and the beliefs in the patient, increasing, therefore, his or her level of adherence.

The frequency of nutrition supplement doses may be important in determining adherence. In a study involving south-east Asian pregnant women, the reduction in the frequency and size of iron supplement doses improved both their adherence with the treatment and, therefore, their haemoglobin status [204]. At least one other study reports similar conclusions. In Indonesian non pregnant women, a descriptive review suggested that "compliance may

be improved when it is not necessary to take tablets on a daily basis", but once-weekly and twice-weekly [205].

Lack of logistical intervention to support patients was suggested to reduce their adherence to treatment regime. But only one evidence was found sustaining this observation. Among Palestinian refugees, complex procedures for the delivery of drugs were deemed to have increased patient drop-out [206].

In treatment adherence, some factors were surprisingly not found to be influential, and quality of life is among them [193]. Hall *et al.* [193], confirmed by Vermeire *et al.* [190], found that socio-economic factors and demographic variables such as sex, marital status, and number of people in the household are also poor indicators of adherence, while, at least in these studies, age remains a controversial predictor [190,193].

Because of the limited knowledge gained about adherence, understanding its patterns and its determinants holds some challenges. For instance, although in two studies [189,207] almost two hundred different doctor-, patient- and encounter-related models have been explored, none of the latter was found to be an ultimate robust predictor of adherence level[189,207]. This unexpected limit induced Lassen *et al.* to conclude that "none of the suggested explanations has accounted for more than a modest part of the observed variations in compliance" [208], and Vermeire [190] shares the same opinion. If this is true, much is still to be discovered in this area of knowledge.

In studies looking at micronutrient supplementation, side effects may be responsible for non-adherence. But some of the available studies show controversial conclusions. Ekstrom *et al.* [209] found that adherence was still low, even when using a form of iron that produces few side effects. Another study seems to contradict these findings. In Norway, pregnant women receiving a similar form of iron supplements complied as well as women taking placebo [210]. The low frequency in reporting side-effects may explain the difficult to explain these results in other studies. In Burma, only three per cent of women stated that side effects were the reason why they stopped taking their supplements [211], consistently with what Vermeire *et al.* [190] found: "side-effects are, surprisingly, only mentioned by five to ten per cent as a reason for non-compliance". In the available literature about supplementation, the role of side effects in relation to adherence remains currently a knowledge gap.

In nutrition supplementation, there is evidence that colour, shape, smell, taste, and the way of supplement provision (i.e. tablet, syrup, capsule or injection) can affect adherence. One study in Mexico found that pregnant women preferred more injections, or red tablets than brown or white tablets, because they felt that red is the colour thought to strengthen the blood [212]. Capsules were preferred by women in Tanzania, because of the association with antibiotics, considered to be the most effective form of treatment [209]. The importance of those adherence determinants may, therefore, vary according to the given contexts and treatments.

Overall, there is sufficient evidence to conclude that identifying the determinants of low adherence is an objective difficulty, and some authors tried, at least, to understand the reasons existing at its root. Claxton *et al.* suggests that adherence "data, based on patient self-reporting, may be erroneous not because patients consciously falsify dosing reports, but because patients may forget about taken or missed". Other authors suggest a different perspective to the problem. Observing how patients ultimately do determine adherence[190], Di Mateo *et al.* [213] identify a close similarity between them and market "consumers", who are often consciously, or unconsciously, "demanding". This approach stresses the need for understanding and interpreting the patient's knowledge, attitude and practice in order to increase treatment adherence. At the consultation, "patients hold sets of beliefs and theories about health and illness"[190], and, therefore, knowing "what sense individuals make of the advice given to them" becomes crucial[190]. On other hand, Di Matteo *et al.* [199] also hypothesizes that "many patients misunderstand, forget, or choose not to follow the recommendations of their health professionals". In these cases, "the offering of medical recommendations that are misunderstood or subsequently forgotten or ignored, is a waste of scarce healthcare resources and suggests a systemic problem" [199].

In nutrition interventions designed for poor settings, adherence determinants were also explored, even if not sufficiently. For instance, in Kenya, a review [214] of a large national programme to supply wasted adults living with HIV with a fortified porridge flours found that cost of public transport to reach the clinic was an important determinant. Without decentralized services, or integrated with the HIV care, the beneficiaries were able to carry home only small amounts of the ration. In the same setting, also other logistic barriers were reported. The intervention suffered from shortage of staff, of counselling rooms, stock-outs,

and lack of alignment between client schedules for the fortified porridge and the ART services. The final perception among the beneficiaries was reported to be that the porridge was not “user-friendly”.

Stigma can be attached to treatment, and, therefore, influencing adherence. The same Kenyan review study [214] concluded that the perception, at community-level, of a food specifically targeting HIV positive people, reduced its consumption. However, low adherence may be due also to other causes. Because of food insecurity in the patient’s households, other family members, not necessarily HIV positive, may have consumed his or her limited supply. This phenomenon was more frequent when the client was a woman. Therefore, in these settings gender is an important adherence determinant. Another study[127] from Kenya and Uganda reached similar conclusions. In these two countries, gender was found to determine nutritional recovery in HIV and TB severely wasted adults, supplemented with RUTF spreads.

The way of proposing the food and its taste were also found to be determinants of adherence. In the Kenyan fortified porridge programme, focus group participants felt “uneasy” with the concept of pre-cooked flour, as well as with the need to use unusually shorter cooking times.

Knowing the current levels of adherence to treatments is as important as accounting for its determinants. The following section quantitatively explores the levels of adherence reported in the recent medical literature.

3.1.3 Recent evidence on adherence

The evidence on patient adherence to medical treatment includes hundreds of empirical studies over the past fifty years. That is due to “chronic disease becoming more prevalent and treatment more dependent on patient self-management” [199].

In 2004, in a large meta-analysis, Di Matteo *et al.* [199] included 569 studies reporting adherence, and finding this to be the highest in HIV, arthritis, gastrointestinal disorders, and cancer treatment, while the lowest adherence was reported in pulmonary disease, diabetes, and sleep care. In the same study, the average non-adherence rate was 24.8 per cent, with the highest rate in patients with HIV, arthritis, gastrointestinal disorders and cancer. This seems to be confirmed by Cramer *et al.* [215], who

found means of non-adherence of 42 and 35 among patients with psychiatric disorders and depression, respectively.

More recently, research on adherence degrees produced controversial conclusions. Dulmen *et al.* [216] considered 38 systematic reviews and found that "many adherence interventions appear to be directed at the chronically ill". While, in another review study [217], it was found that "in general, adherence rates are higher among patients with acute conditions compared to patients with chronic diseases", and apparently, in these patients, adherence "is disappointingly low, dropping most dramatically after the first six months of therapy" [218]. In 2007, based on a set of contradictory evidence [187,190,219,220], it was suggested that "the research about adherence (levels) seems to have got stuck"[216].

The literature about adherence levels to diet-based treatments is poor, and only one review study on dietary adherence was found. In a gluten-free food regimen, Hall *et al.* [193] reports that more than 60 per cent of the adults, all with celiac disease, were not following the dietetic prescriptions. However, "lack of comparability between studies, in terms of design, methods, definitions and measurement of adherence" may weaken this study conclusions[193]. It can be concluded that well documented levels of adherence are, therefore, limited [221].

Although its current levels could not be ultimately established, adherence to treatment was measured with a variety of methods, which were experimented in a large number of studies. The latter are summarized in the following section.

3.1.4 Measurement of adherence

Measuring adherence to treatment in the correct way is important. Therefore, its accurate estimation cannot be over-emphasized. The following sub-sections explore both the theory and the practice of adherence measuring.

3.1.4.1 Models of adherence and its determinants

The available literature reports *models* to estimate adherence to treatment, and also calls them *approaches* or *frameworks*. These are often numerous, complex and sometime overlapping. Since a consensus was not achieved, researchers grouped them into categories or clusters, summarized in the following paragraphs.

In one review study [213], three models, namely the Health Belief model, the Theory of Planned Behavior, and the Transtheoretical approach, are summarized in the following way: common components of these frameworks "involve health professional-patient communication, patients' cognitive and social processes (e.g., beliefs, norms), and patients' resources (e.g., financial, psychological, and social support)".

Other researchers preferred alternative approaches. Roter *et al.* clustered the ways to measure adherence according to the following four theories: the Behavioural approach, the Educational model, the Affective framework, or combinations of all these [222]. Dulmen *et al.* [216] grouped the models as Technical, Behavioural, Educational, Social and Multifaceted.

In reading of the vast available literature, and aware of its limits, I identified four general model groups to measure adherence to treatment. In the first one, the correlation between health outcomes and the dosages, the packaging or the frequency of the drug intake, are often at the centre of the measurement. This approach is for instance typical in the often so-called *technical models*. In models considered *behavioural*, the correlation between health outcomes and memory aids and reminders for the patient (via telephone, computer or by home visits) is explored. From the perspective of the latter theory, "human behaviour depends on stimuli or cues that elicit certain responses and on the rewards that reinforce behaviour" [216].

The third model is referring to *Educational* elements or "cognitive didactic approaches", that include "teaching and providing knowledge" [216], and are defined as "educational interventions given with the intent of improving the person's ability to manage his or her disease " [223]. These models involve "different ways to educate patients: individual versus group education, face to face contact, audio-visually, in writing, by telephone, by e-mail or via home visits" [216]. Collaborative Care can be considered part of the Educational Model, and was defined as a systematic approach involving any figure of "health professionals or other care providers"[224].

Social models, belonging to the fourth group, are more focused on the support that the environment of the patient can provide. In a large review study, Di Matteo [213] found that "practical, emotional or undifferentiated" social supports had the strongest relationship with adherence. However, it is "not yet understood how social support contributes to

health, and which factors moderate and mediate this relationship" [216]. Multifaceted models include different approaches. Dulmen *et al.* [216] describe them as "effective for long-term care", but also "exceedingly complex and labour-intensive" to measure.

Despite the available models, measuring adherence adequately, remains challenging [216]. This is for at least two reasons. One is that there is a scarcity of comparative studies explicitly contrasting theoretical models or their components [216]. The second one is that "research into a phenomenon as complex as adherence is inevitably fragmented" [190], therefore "a model or theory to integrate the different studies" to support its adequate measuring was not found [190]. However, some authors conclude that "innovations in theory and practice are badly needed" [216].

3.1.4.2 Ways of measuring adherence

Consensus on one model to understand and explain treatment adherence levels is missing. The same is true for a standardized protocol meant to measure them with accuracy [194]. Most studies report the method which they applied, but, in general, their degree of complexity is high[216]. This is explained by Di Matteo *et al.* in the following way: "there is no one adherence measure against which to calibrate others, making concurrent validation impossible" [213]. The little documented in the literature is reported in this section.

Measures of adherence can be direct or indirect. The former consists only of direct observation, is "practical only in single-dose therapy, intermittent administration and hospitalized patients" [225], and is carried out whenever possible by an "independent observer"[194]. Indirect measures may be taken in many more ways, applied individually or in combination [194]. These include medical records and/or charts, interviews, self-reports, collateral reports, electronic monitoring, tests based on Likert scales, pharmacy reports, assessments of the motivation to adhere, pill counts or checks on container refilling, diaries, physical and biochemical tests [194,213,216]. The latter usually consists of "detection of a chemical (metabolite or marker) in a body fluid (blood, urine)" [194]. Although this is an objective approach, methods based on body fluid are still considered indirect [194], and can be resource demanding.

However, most of the listed methods present flaws. For instance, "interviews and all self-report methods are vulnerable to overestimates of compliance and underestimates of non-compliance" [190]. When comparing methods, "self-reports have been shown to overestimate

adherence by as much as 200 per cent, compared with biochemical measures" [194]. Krueger *et al.* [194] explains this phenomenon based on "the patient's desire to appear compliant", and suggesting that "patients do not remember exactly when they took their medication or record the times at which they were supposed to take it". "Drugs counts also appear to overestimate adherence, because patients may discard any remaining pills if they know that a count will be conducted" [194]. Vermeire *et al.* [190] concluded that "interviews and all self-report methods are vulnerable to overestimates of compliance and underestimates of non-compliance". Also the method based on the refill record is not exempt of issues. In the available literature it was found that this is a "reliable method of determining whether someone picked up the prescription, but it provides no information about a patient's actual medication use" [194].

Methods in studies looking at dietetic adherence, may face additional challenges. Unfortunately, despite the large number of studies looking at the efficacy of prescribed dietetic patterns or supplements, in most existing studies, the differences in adherence levels are not discussed [226]. When documentation is available, the methods were described in the following way. Dietetic assessments are often conducted by an expert, and are usually based on an interview or a food diary, considered the most objective, non-invasive method of measuring adherence [193,202,227,228].

Analysis of these measurements must often take into account the synergic effects or interactions between nutrients or foods that comprise the diet [229–231]. This can be an additional issue. To solve this, interactions indexes are in use, often based on food groups. This approach requires food categorisation processes, which are complex when evaluating mixed dishes [231]. Despite these difficulties[232], grouping foods to obtain index scores remain "a very useful method" to increase the accuracy of dietetic adherence measurement[232].

3.1.4.3 Measuring adherence in low-resources contexts

The studies measuring dietetic adherence in emergency or low-resource contexts are few, but increasing in number. This section reports studies, which described how adherence to micronutrient supplementation, fortified staple food supply, and RUF-based treatment was measured.

In a Kenyan refugee camp, a study [226] explored the factors influencing the adherence to a micronutrient supplementation programme using qualitative methods. These included

focus group and key informant interviews. The tools used during the survey included free lists, ranking exercises, scenarios, and open-ended questions. The surveys were conducted in the traditional languages of the interviewees, and interpreters were used throughout the research activities.

In the same country, in 2009, a report reviewed a large national programme called "food-by-prescription" [214]. Thanks to this intervention, in an out-patient setting, wasted adults received fortified porridge flour. Also in this study, qualitative measures included interviews and focus groups. The data were matched with an index called length of stay, defined as "total time that a client remained in the food by prescription program before s/he exited". The time, therefore, comprised the days on active and non-active treatment, periods of missed food supplementation, and non-adherence. The same year, another large report on the same type of programme was reviewed by Greenaway [233] using the same qualitative methods.

Few studies documented adherence to nutritional therapy using lipid-based, ready-to-use pastes. In Senegal, Diop *et al.* [71] compared the efficacy of the therapeutic formula milk F100 (described in section 1.2) and the peanut-based RUTF formula in children under five years of age. However, the children were consuming the RUTF in the feeding centre attached to a clinic. A direct measurement of adherence, as direct observation, was, therefore, simple to implement, but its results less applicable when generalised to other settings.

In Malawi, Ndekha *et al.* [116] also compared the same RUTF formula but with a fortified porridge flour in wasted adults living with HIV. Adherence was measured only when study participants failed to return to scheduled clinic visits for antiretroviral therapy. In these cases, they were visited at home and information regarding adherence were collected with interviews. Data about their treatment, clinical status and anthropometry were included. At completion of the trial data collection, "social scientists from the University of Malawi, who were not involved in any other aspect of the study, led open ended focus group discussions to explore the use, acceptability, and sharing of the food supplements and to assess dietary compliance".

In the Democratic Republic of Congo, Bisimwa *et al.* [234] assessed the effectiveness of a fortified soybean-maize-sorghum RUCF paste. This was compared with fortified corn soy

blend porridge. The prevalence of underweight and stunting, in infants, was the primary outcome of this study. Adherence to the complementary feeding instructions was measured using questionnaires, asking the mothers for the amount of food the children were consuming, and counting the containers of either RUCF (sachets) or porridge (bags) already used.

Seven other studies [62,101,124,125,128,129,152] looking at different aspects of nutrition interventions using lipid-based, ready-to-use pastes highlighted the importance of measuring adherence in order to interpret the results. Surprisingly, this outcome measure was not part of their method and/or result sections.

The documented ways to measure adherence to nutritional treatment in limited-resource settings are limited in number. This conclusion is consistent with a recent USAID document looking into ways to improve food aid [109], and reading: “many, if not most, studies fail to monitor compliance, which is a key factor in recovery with the use of nutritionally enhanced products”. However, the current situation is improved by the contribution from the adherence study described in the following sections. This includes the description of the overall and specific settings of the study, its method, its results, followed by their discussion and conclusions.

3.2 The overall and specific setting of the study

This study took place in Kenya, East Africa. The following sub-sections first introduce the reader to the generalities of this country, including its nutrition, health and HIV/TB profiles, and then describe the specificities of the study setting.

Figure 16 - Map of Kenya

Source: FAO 2005 [237]

3.2.1 Kenya: generalities and nutrition-related facts

With its typical tropical climate, Kenya is located in Eastern Africa, sharing its borders with Somalia and Ethiopia to the North, Uganda to the west and Tanzania to the South. Nairobi is the capital and Mombasa is the second largest city and the main harbour of the region, located on the Indian Ocean (East side of the country). Kisumu is the third town and the main port on the Lake Victoria.

According to the latest UN data, in 2009 Kenya had a population of almost forty millions, with a density of 68.6 person per square kilometre [235], which is close to that reported for neighbouring countries. The same year, the Kenyan gross domestic product was approximately 30 million US dollars, showing an increase in the last years of approximately 2.6 per cent per year [235]. Basic primary care is provided at healthcare centres and dispensaries. Sub-district, district and provincial hospitals provide secondary care, such as integrated curative and rehabilitative care.

The recent drought and the food crisis in the whole region had large negative impacts on most sectors [236]. Despite this, the World Bank recently praised the Kenyan efforts to improve gender- and water-related interventions [236].

Kenya is currently a rural country. In 2009, only 22 per cent of the population lived in urban areas, with an annual increase of 4.2 per cent. In 2010, the life expectancy increased up to 56 years, which is higher than the average in the region. In the same year, the national under-five mortality rate was 128 per 1,000 live births[41], which is far higher than the MDG target of 35 per 1,000 live births, set to be reached by 2015. The same sources suggest that the stunting, underweight and wasting prevalences of children under five years of age are stable (35, 16 and 7 per cent, respectively). Insufficient breastfeeding practice is still an issue, with only 32 per cent of children less than six months of age being exclusively breastfed [41]. Maize is the basic staple of the Kenyan diet. Ugali, the main dish, is a thick porridge of maize meal that is usually eaten with a sauce of vegetables or meat, or accompanied with fermented milk [237].

3.2.2 Kenya and HIV: prevalence and response

Currently, the progression of the HIV/AIDS epidemic is a major cause of poverty and food insecurity, "killing active adults, devastating families and increasing the number of orphans" [237]. The national HIV prevalence in 2007 was estimated at 7.4 per cent in the age group of 15 to 49 years, and at 7.1 per cent in the age group from 15 to 64 [238]. An estimated 70 per cent of HIV infected people live in rural areas [238]. However, in this country, the syndrome is considered by UNAIDS as "geographically heterogeneous" [238]. In Kenya, Nyanza province had the highest prevalence (13.9 per cent) in 2010 [239].

The Government launched a Strategic Plan (KNASP III) 2009/2010 - 2012/2013 that seeks to respond to the HIV public health concern. The intervention focuses on the reduction of the number of new infections by 50 per cent, on the reduction of HIV related mortality by 25 per cent, and drastically increasing access to treatment and care services, for those who are in need [238]. In 2012, in Nyanza Province, "the initial years of rapid HIV service expansion coincided with a drop in adult mortality by a third" [240].

3.2.3 Kenya and TB: prevalence and response

Kenya ranks 13th on the list of 22 high-burden tuberculosis (TB) countries in the world and has the fifth highest burden in Africa. According to the WHO Global TB Report 2009 [241], Kenya had more than approximately 132,000 new TB cases and an incidence rate of 142 new sputum smear-positive cases per 100,000 population.

Kenya continues to treat more and more TB patients each year. However, widespread co-infection with HIV (close to 48 per cent of new TB patients) makes TB treatment difficult. While the number of new cases appears to be declining, the number of patients requiring re-treatment has increased [241].

In 2007, the government demonstrated increased political commitment by upgrading the division dealing with TB health issues within the MOH, and with increased funding for TB control. A larger proportion of TB patients benefited from improved "Directly Observed Treatment Short course" services (DOTS). The programme implements TB and HIV/ AIDS treatment services, community-based DOTS, and public-private mix DOTS, as well as activities to address multi-drug resistant TB programmes [241].

The international NGO Médecins Sans Frontières / Doctors Without Borders (MSF) has two large HIV and TB programmes in Kenya, both in the capital Nairobi and in Nyanza area.

3.2.4 MSF: the HIV/TB programme in Nyanza Province

Since the beginning of the 1990s, MSF has supported the local national health services in Homa Bay, Nyanza Province (Kenya). At the time of this study, the MSF intervention supported the district hospital and four primary health care facilities. The district referral hospital offers health services to a rural area with approximately 300,000 inhabitants[127]. In collaboration with the Ministry of Health, MSF provided outpatient and inpatient HIV and TB care [127]. With the aid of MSF, when necessary, patients were also referred and transported for hospitalization [127].

In the MSF/MoH programme, the eligibility criteria for starting a combination of ART were as recommended by the WHO guidelines (2006). The criteria admit all patients with WHO clinical stage 4, or patients with CD4 counts of less than 200 cells/mm^3 [127]. In the MSF intervention, CD4 cell counts were monitored at ART start, at six months, and yearly after the first 12 months of therapy. No routine viral load monitoring was performed [127]. Once a new patient was eligible for ART, he/she received three pre-ART counselling sessions: first, on the day of ART eligibility assessment; second, two weeks later; and third, one to two weeks thereafter. The process took between 15 to 30 days, but may have varied according to patient clinical status or readiness to initiate ART [127].

The record system of the HIV programme included the software database FUCHIA, designed to hold data from MSF HIV programmes around the world.

3.2.5 The MSF nutrition programme

In mid-2006, MSF, in collaboration with the MoH, began providing RUTF to all severely malnourished patients attending the HIV/TB programme in Homa Bay[127]. The same intervention started simultaneously in the Nairobi slum of Mathare [127]. The RUTF provided was an energy dense peanut-based spread (Plumpy'nut®, Nutriset, Malaunay, France), originally designed for the treatment of children with SAM [127] and thoroughly described in section 1.3 at page 61 of this thesis.

Only patients diagnosed with WHO stage 3 or 4 conditions were enrolled in the Homa Bay HIV / TB nutrition programme [127]. Among these, malnourished adults, aged 15 years or older, received therapeutic feeding if their BMI was less than 17 kg/m^2, or they had bilateral pitting oedema in the lower extremities [127].

Enrolled patients received four sachets of RUTF (2,000 kcal) per day in the outpatient clinic, and were clinically assessed every two weeks or monthly before renewal of the RUTF prescription [127].

During the counselling sessions frequently asked questions from the patients and the caretakers about the frequency and the amount of RUTF to consume were answered. However, no training and counselling material were supplied to support the health staff members in this activity. During the first or the following visits, the capacity of swallowing or accepting the RUTF was not systematically assessed by the health staff, despite this is part of the guidelines of the treatment of SAM [97]. Although wasted children with medical complications were enrolled - in accordance with the same guidelines [97] – into a residential therapeutic feeding programme based at the district hospital, adults and adolescents older than 15 years of age were included only in the out-patient programme.

Patients were defined as "cured" and discharged [127] from treatment using the criterion of BMI above or equal to 18 kg/m^2 and no oedema for at least two consecutive weeks. Therefore, patients meeting the predefined exit criterion were discharged, after full clinical review, at any time after enrolment [127].

Patients who were unresponsive ("uncured" according to the protocol definition[127]) to nutritional therapy after six months of treatment (not reaching BMI ≥ 18 kg/m^2) were reviewed by a physician for further investigations and management [127]. After clinical assessment to exclude presence of undiagnosed pathologies, they were discharged from the nutrition programme, referred to patient support groups, and given a supply of corn-soya blend, beans and oil, through local aid agencies.

A written protocol reported in detail the contents of the nutrition programme, and was available for the programme staff. However, at the time of the study, no training was provided to the health staff to ease its application.

From January 2008 to March 2009, MSF admitted 782 malnourished adults into the therapeutic nutrition programme, and the monthly mean weight gain was 1.8 (SD 0.5) g/kg/d. Data prior to 2008 was not available.

After two years from the beginning of the nutrition programme, a tailored database, hosted by the software EpiData-Entry, was designed and tailored for the Homa Bay HIV nutrition programme. The records included also the FUCHIA patient code.

3.2.6 The Ahoua (*et al.*) study

A retrospective study, conducted by Ahoua *et al.* [127], discussed the results from the cohort analysis of east African adult patients enrolled in MSF interventions, from 2006 to 2008. Beside Homa bay, the study also included data from the MSF programme in Mathare, a large Nairobi slum, and from Arua town, in Uganda. The three sites used the same protocols for HIV / TB treatment and for the nutritional rehabilitation of their patients' cohorts (see section 3.2.4 and 3.2.5).

Within the nutrition programme, the study focused on predictors of treatment failure. The study used multiple logistic regression, and four failure outcome categories: patients "discharged uncured" (remaining in the programme for longer than six months), "defaulting", "dead" or discharged because of "other reasons". The following section reports the main results and the study conclusions. Unfortunately, the article presents the data for the three MSF sub-programmes altogether, rather than unpacking them per site.

In the three MSF interventions, 15.4 per cent (n=8,685) of the HIV-positive adults were enrolled in the nutrition programme. On day one of the treatment, their BMI was 15.8 kg/m^2 (IQR 14.9-16.4), and only 12 per cent of the cohort had previously received ART drugs. At the end of the study, only 47.7 per cent (total n=1,106) of the patients were considered "cured", and their follow-up time lasted approximately four months (IQR 2.2-6.1). Forty-eight per cent of the patients were "non-cured within six months", of whom 11.9 and 22.6 per cent died or defaulted from care. More than four per cent were discharged because of "other reasons". Increased risk of nutrition programme failure was found to be higher in men (OR = 1.5, 95 per cent CI 1.2-2.0), in patients with BMI below 16 kg/m^2 at study enrolment (OR = 2.2, 95 per cent CI 1.7-2.8), and in patients who did not start ART when eligible (OR = 4.5, 95 per cent CI 2.7-7.7), as well as for those who were ineligible for ART at enrolment (OR = 1.6, 95 per cent CI 1.0-2.5). The weight gain among the cured patients was 1.6 g/kg/d.

The study concluded that the administration of ART together with RUTF increases the chances of nutritional recovery of the study cohort, that the cure rates varied widely and that early nutritional support with RUTF seemed to be more effective when provided in the early stages of wasting. However, the percentage of not cured was high. For this reason, the authors voice "the need to clearly define and evaluate the most effective ways of administering" therapeutic nutrition care, based on RUTF, in wasted adults living with HIV. No measurement of adherence was included in this study.

Therefore, in this chapter, aware of the different models for understanding adherence and their limitations described in the literature, I investigate the adherence and explore the potential key barriers existing in the Homa Bay nutrition programme, in order to shed some light on its low nutritional rehabilitation rate.

3.3 Objectives of the study

Aim of the study:	Development of a method to understand how current formulations of RUF affect its usage
Specific objective:	To investigate adherence with RUTF in a HIV/TB therapeutic

nutrition programme in Kenya

Research questions: (i) what is the adherence to a protocol using a specific RUTF (Plumpy'nut) among malnourished adults living with HIV?

(ii) what are the key barriers to patient adherence?

The present study is among the first to qualitatively investigate adherence with nutritional protocols based on RUTF that aims at rehabilitating malnourished HIV adults. The following sections report the results according to COREQ guidelines [242].

3.4 Methods

3.4.1 Study setting

The setting of the study was described in sections 3.2.4, 3.2.5 and 3.2.6.

3.4.2 Study design

In this study, I applied three qualitative methods based on focus groups, interviews and direct observations. I considered their results valid, when found to be consistent, one to another. Focus group discussions involved patients and caretakers, and one separate session with members of MoH/MSF medical staff. Semi-structured interviews were administered one-to-one to patients. Direct, unobtrusive, observations of the Plumpy'nut® distribution and consumption occurred in the HIV/TB wards. The questionnaires and the focus group discussions used a variety of techniques including free listing, ranking exercises and open-ended questions (see footnotes in Table 12).

3.4.2.1 Questionnaires and focus group guides

Two guides were developed and piloted for use in the focus groups: one for patients and caretakers, and one for the health staff members. The guides and questionnaires covered four topics:

(1) information provided to patients about the recommended use and consumption of Plumpy'nut®;
(2) knowledge and attitude of patients about the role of Plumpy'nut® in their therapy;

(3) dietary practices and Plumpy'nut® consumption;

(4) patient' and caretaker's experience of the Plumpy'nut® distribution system.

A checklist for the direct observations was developed, and covered the ways of consuming Plumpy'nut®, their advantages and disadvantages, together with the role of the caretaker.

All the focus groups were recorded on tape, transcribed and additional notes allowed the checking of information that was not clear from the recordings. The focus groups and interviews did not last more than one and a half hours, and one hour, respectively. The direct observation sessions lasted between thirty minutes and one hour. A small number of photographs were taken with the informed consent of the patients.

3.4.2.2 The research team and the relation with the subjects

The focus groups discussions and interviews were conducted in the Luo language. Two native speakers, a female and a male, were recruited as interpreters and provided with two days training on the study and methods to be used. Time for familiarization with the study guides was provided.

As principal researcher, I am a Caucasian male who was trained in public health nutrition at MSc level, and I was not a MSF employee. I attended all focus groups sessions and benefited from simultaneous translation by an interpreter. I personally facilitated, in English, the focus group discussion with the health staff, and subsequently transcribed the recorded tape myself. Other discussions were facilitated by the study interpreters. Discussion transcripts were not returned to the study members for comments or corrections. All participants were provided with information about the study and assured that clinical services or RUTF provision would not be affected by refusal to participate.

3.4.2.3 Identification of the common themes

I manually coded the focus group discussion transcripts, highlighting key words, key concepts and any minor or contradictory themes, using both hard- and soft-copies, marking methods and mind-mapping approaches. I regularly reviewed the records of the direct observations, and I summarised the found pieces of evidence. I entered the quantitative data from the interviews and the clinical and socio-economic profile of the focus group

participants in EpiInfo version 3.4.3 and analyzed the same in Stata version 8.

I subsequently prepared detailed tables for each identified theme and its associated sub-themes. The theme tables contained separate columns referring to the evidence obtained on each theme using one of the three research methods (see Table 12). This allowed triangulation of evidence, comparison and discussion of the common themes that emerged. Following this process the themes and sub-themes from the separate tables were compiled and overall conclusions drawn. Conclusions and associated recommendations were discussed with the health and management staff of the programme during a feedback process.

3.4.2.4 Subjects recruitment and sampling

The study subjects, enrolled at the MoH/MSF HIV/TB programme in Homa Bay health district, Nyanza Province, Kenya, came from three groups: patients enrolled in the program (some already nutritionally rehabilitated); their caretakers; and medical staff (counsellors, nurses and clinical officers). Patients younger than 15 years of age were not admitted into the study group. The patients were recruited either at the MoH/MSF HIV clinic A and B at the Homa Bay Hospital, or from TB wards 7 and 8 of the same hospital.

The study followed a non-probabilistic, purposive, heterogeneity, non proportional quota sampling system. Data saturation was achieved after approximately two thirds of the study; however, recruitment continued along the whole planned period (3 weeks). During the study time, the patients, coming for their usual routine visit, were invited to participate by the nurse in charge of the nutrition programme. All the health staff working at the clinic during the study agreed to participate.

All the focus group discussions and interviews occurred in a quiet area within the HIV clinic compound in the presence of the researcher and his assistants only, whereas the direct observations were performed in the TB multi-drug resistance ward at the Homa Bay general hospital.

3.5 Results

3.5.1 Study group characteristics

Table 10 provides descriptive data on the 46 patient participants. Thirty-four were still under treatment with Plumpy'nut®. More than half of them were females and the average age was thirty-three years. All patients were married and the majority had their spouse still alive while 12 out of the 46 patients were widowers. All subjects who were approached agreed to participate in the study and provided informed written consent. Data about the duration of nutritional rehabilitation was not availed by MSF.

Table 10- Profile of patient participants.

Characteristic (n=46)	Participants (n and percentage, if appropriate)
Male	18 (39%)
Female	28 (61%)
Age (years)	33.3
Married (missing records = 1)	45 (100%)
Spouse alive	33 (73%)
Widowers	12 (27%)
Mean number of children* (missing records = 1)	3.0
Serological status (missing records = 6)	
HIV positive	24 (60%)
HIV positive and TB sputum-positive	16 (40%)
Nutritional rehabilitation (missing records = 1)	
Enrolled in the nutrition programme at the time of the study	
• *not malnourished* † *anymore*	15 (33%)
• *currently malnourished*	19‡ (42%)
Discharged by the time of the study	11 (25%)

* NB: age not specified.
† BMI ≥17 and/or MUAC ≥160.
‡ This group included 13 outpatients and 6 inpatients. The inpatients were from the TB multi-drug resistance ward.

Table 11 summarises the methods used and the number of patients, carers and health staff

participants.

Twenty-two current and ex-patients received one-to-one interviews and 18 participated in focus group discussions. Six inpatients were directly observed. Two carers were recruited to participate in focus group discussions. Eight MoH/MSF employees participated in the focus groups with the medical staff (counsellors, nurses and medical doctors). None of the subjects were involved in more than one data collection method.

Among the outpatients (n=13) who were still malnourished, 6 travelled to the clinic without a carer on the day of the study (2 missing data). Only one walked while the rest took public transport and the average time to reach the clinic was almost two hours. The 6 in-patients recruited for the direct observations were found in the TB wards of the Homa Bay Hospital and they were all HIV positive; two of them were multi drug resistant and their appetite might have been affected by their TB status and/or HIV status plus specific drug side-effects.

Table 11 - Summary of methods and participants.

Method	Participants* (n=56)
Individual interviews with current and ex-patients	22
5 focus group discussions from 3 to 5 participants, including:	
Current and ex-patients	18
Carers	2
Direct observations on individual in-patients and their carers role	6
1 focus group discussion with health staff	8

* None of the study subjects participated in more than one method.

Table 12- Summary of key themes and sub-themes.

Theme	*Individual interviews*	*Focus group discussions†*	*Direct observations*
Adherence *with Plumpy'nut®*			
• Only approximately half of the patients complied with the prescribed amount	X‡	-	X
Positive aspects *reported about Plumpy'nut® - Participants think that:*			
• It is similar to a drug rather than a food, in terms of both usage and role in the recovery	X‡§	X	-
• It "brings strength"	X‡§	X	-
• It "allows to go back to work"	X‡§	X	-
• Increases weight gain	X‡§	X	
• Decreases the feeling of hunger	X‡§	X	-
• Has a smell and packaging which are well accepted	X‡§	X	X
• Offers the possibility to mix it with other food and therefore reduce:	X‡§	X	X
o diet boredom	X‡	X§¶	-
o nausea	X‡	X§¶	X
Negative aspects *reported about Plumpy'nut® - Participants think that:*			
• It can cause nausea and vomiting	*X‡§*	*X*	*X*
• First 3 to 4 days of consumption are crucial for adherence, then later it becomes easier	-	*X*	*X*
• The taste is:			
o too sweet	*X‡§*	*X§¶*	-
o too oily	*X‡§*	*X§¶*	-
o too salty	*X‡§*	*X§¶*	-
• Consistency should be more liquid or like a biscuit or a powder (milk powder)	*X‡§*	*X*	-
• It comprises a monotonous diet, leading to boredom	*X‡§*	*X*	-
Sharing Plumpy'nut® *with both other adults and/or children is a common practice*	*X‡*	*X*	-
Reasons for sharing:			

Theme	*Individual interviews*	*Focus group discussions†*	*Direct observations*
• food insecurity in the household	-	*X*[§]	-
• children like it	*X*[‡§]	*X*[§]	-
• the partner or relative is ill and/or HIV positive but not malnourished (energy booster)	-	*X*[§]	-
Mixing Plumpy'nut® with foods *is a common practice*	*X*	*X*	*X*
Reasons for mixing:			
• to reduce monotony of the diet	X[‡§]	X[§]	X
• to reduce nausea, vomit, salty taste	X[‡§]	X[§]	X
• because the Plumpy'nut® has separated into oil and solid phases	X[‡§]	-	-
• because Plumpy'nut® with water reminds participants of a traditional food	-	X[§]	-
• because it was suggested by the health staff	-	X[§]	-
Knowledge and attitudes of medical staff			
Medical staff expressed doubts about the positive role played by Plumpy'nut® in nutritional rehabilitation; ART was perceived as much more important	-	*X*	-
Patient counselling			
• Counselling messages focus on: o human nutrition (e.g. "proteins are available in meat, eggs and cheese") o improvement of general conditions when consuming Plumpy'nut® (weight gain, appetite, strength)	*X*[‡§]	*X*[§¶]	-
• Most patients did not know the relationship that exists between HIV infection, their thinness and their ART therapy.	*X*[‡§]	*X*[§]	-
• Staff declared that they did not know what counselling to provide to patients with severe clinical conditions (e.g. oral thrush)	*X*[‡§]	*X*[§]	*X*
• Most patients do not receive routine information about why, when and how to consume Plumpy'nut®; when this happens, it comes from individual initiative of the health staff	*X*[‡§]	*X*[§]	*X*
Distribution system *for Plumpy'nut®*			
• Half of the patients still under nutritional rehabilitation come to the HIV clinic without a	*X*[‡]	*X*	-

Theme	*Individual interviews*	*Focus group discussions†*	*Direct observations*
caretaker			
• The patients cannot carry more than a 2 weeks supply of Plumpy'nut® (approximately 6 kg) instead of the whole month's supply	*X‡*	*X*	*X*
• The appointment schedule for ART or clinical checks is monthly in most cases, therefore patients or caretakers do not come back to collect the missing 2 weeks supply of Plumpy'nut®	*X‡*	*X*	-
• Very weak patients are in absolute need of the caretaker even to open the sachets, to mix it with other food (when needed) and consume it	-	-	X
• Bulky supply (6 to 12 kg) and branded container (box) are very noticeable and associated with stigma within the community	X‡	X	X

* None of the study subjects participated in more than one method.

† The focus groups involved either patients together with caretakers (5 groups, with 3 to 5 participants), or health staff members (1 group with 8 participants).

‡ Tool used: closed and/or open questions.

§ Tool used: free listing.

¶ Tool used: ranking exercise to select the main themes reported here.

** ART drugs change certain flavour perception.

3.5.2 Understanding adherence

The following sections summarize the key themes emerging from the analysis of the results. Overall, only 14 out of 22 interviewed patients reported adhering with the prescribed amount of Plumpy'nut®.

3.5.2.1 Perceptions about Plumpy'nut®

Table 12 lists the aspects which may both enhance or decrease the adherence with Plumpy'nut®, and were mentioned during the majority of focus groups and interviews. It was frequently reported that Plumpy'nut® can be "associated with a drug" (same role and effect of a drug), "brings (physical) strength" and "allows to go back to work". Increases in weight gain were reported, and feelings of hunger said to decrease. The positive feelings about use of the product can be summarised by the quote: "ART is a drug to fight the infections, but does not give strength like Plumpy'nut® to go back to work".

Turning to the negative perceptions of participants, some patients complained that the taste of Plumpy'nut® was responsible for nausea and the vomiting. Participants also argued that the "first three or four days are the most critical ones" and that "after then, it becomes easier" to adhere to the prescription. Among the patients interviewed, only one out of 40 mentioned oral thrushes as the main cause for low acceptability. In contrast, the health staff focus group voiced that the initial clinical conditions including swallowing capacity are crucial for the patients' adherence. The interviewees provided suggestions about how to improve the product (see Table 12).

The medical staff expressed doubts about the role of Plumpy'nut®, in promoting weight gain, since "ART is far more important in severely malnourished patients".

3.5.2.2 Sharing practices

Adherence was found to be closely linked with food sharing practices. More than half (14 out of 22) of the interviewed patients reported sharing the Plumpy'nut® with children and other adults, and this was confirmed by most focus groups. The medical staff was particularly concerned about the sharing practice at the community level, based on their observation that, "…in the hospital wards, it is common".

In two of the focus groups, patients reported incidents of Plumpy'nut® trading or selling. This, however, seems to be limited to school children, because, among adults the product was associated with HIV treatment, and thus potentially stigmatising.

The majority of the patients, who declared that they tried to prevent sharing ("hiding the product in the closet from children"; "…or from adults"), did so because Plumpy'nut® was considered part of the "medical drug prescription". Only one interviewee reported that Plumpy'nut® could be actually harmful for an HIV negative person.

One member of the medical staff suggested that Plumpy'nut® is so important for the household food security that sharing represents a strategy to delay the moment of programme discharge.

3.5.2.3 Mixing Plumpy'nut® with other foods

Only one patient reported exclusively consuming Plumpy'nut®, while mixing Plumpy'nut® with other food was a common practice mainly with local staple starchy food (*ugali*), fresh vegetables, fish, rice, cereals, legumes, meat, cooked vegetables (*sukuma wiki*), and chapatti (in order of reported frequencies).

Monotony of diet, nausea, vomiting or salty taste was the main reasons for mixing. Stirring Plumpy'nut® into hot water produces something that is similar to a popular, peanut-based, traditional food (*ogila*).

Some others mentioned that "once you start mixing the Plumpy'nut®, it is hard to go back and eat it alone". Members of the medical staff suggested (contrary to programme recommendations) that patients with severe clinical conditions (e.g. oral thrush) should mix the Plumpy'nut® with tea.

3.5.3 Key barriers to adherence

3.5.3.1 Inability to transport ration

Physical weakness, absence of a carer during the collection of supplies, cost of transport, and stigma were key barriers to adherence.

The prescribed supply of Plumpy'nut® per outpatient was monthly and weighed

approximately 12 kilograms. A malnourished outpatient without a carer did not have strength enough to carry such weight. Therefore, the outpatients were invited to take half the monthly ration and come back to collect the second half of the supply in two weeks time. Health staff members reported that most patients could not afford to travel twice a month to the clinic.

It can be speculated that these patients spread out the two weeks provision along the entire month. This is consistent with the reports of many patients. No data could be found on how many patients came back to collect the missing mid-month supply or the relationship with defaulting and survival.

3.5.3.2 Stigma associated with therapeutic foods

In a region where HIV-related secondary malnutrition is common and treated with Plumpy'nut®, this product has become strongly associated to HIV.

For this reason many patients were reluctant to walk home with boxes reading the brand name (Plumpy'nut®). One patient said "I can disguise the ART tablets saying that they cure something else, but I cannot disguise Plumpy'nut® because a month's supply is too bulky and visible".

3.5.3.3 Clinical status and role of the carer

Among the in-patients who were directly observed, all the ones with a severe clinical condition could not adhere to the prescribed amount. Two of these died during the course of the study. Alternative therapeutic diets, such as therapeutic liquid milks (formulas F75 and F100), whose intake may have been easier for severely ill patients, were not available.

It was reported and observed that in-patients in the ward with the most severe clinical conditions can consume Plumpy'nut® only if mixed with other suitable food (water or porridge for example). This requires assistance from the carer. Patients with severe clinical conditions were so weak that they did not have sufficient strength even to open the sachet and to mix the product with the foods.

The Focus Group Discussion with the health staff voiced that often malnourished patients showed swallowing difficulties due to extended oral thrush. The MoH/MSF protocol for therapeutic nutrition did not require the medical staff to report the presence or the degree of swallowing difficulty. Therefore, quantitative data were not available, and written

prescription reports of oral thrush treatement could not be availed for the research. However, direct observation confirmed that most malnourished patients enrolled to the ward showed evident pain in swallowing any type of food, including RUTF in partially diluted form.

3.6 Discussion

This study indicated that adherence with therapeutic feeding within this HIV programme is likely to be low. We have identified a number of issues that may reduce the consumption of RUTF to below the prescribed level.

Although the nature of the study setting might have affected the patients' response, some of the findings are likely to be generalisable to other HIV and adult nutrition programmes that use this specific therapeutic food and a similar nutritional protocol.

This study identified two groups of factors, which limit specifically RUTF-based protocol adherence:

a. factors directly related to the *product* design, and

b. factors related to *programme* design.

3.6.1 Factors related to product design

Factors intrinsic to the product design are many, and their nature is varied. Their interpretation must take into account the origin of this RUTF. Although widely used for other patient groups, it is important to note that Plumpy'nut® was designed for treating severe acute malnutrition in children.

There is evidence [243] to suggest that reported symptoms such as nausea and vomiting when eating the RUTF could be related to the drug treatment too. The taste of Plumpy'nut® was not considered suitable by many adult patients and, therefore, they often reduced intake or mixed it with other foods. Plumpy'nut® is fortified with KCl, which has a salty bitter taste (private communication: Briend, February 2014). The practice of mixing may compromise the efficacy of RUTF by reducing overall energy and nutrient intake, and delaying nutrition rehabilitation.

Despite the problems of taste and consistency acceptability, the results of this research

suggested that most patients valued the nutritional therapy provided by Plumpy'nut®. Their attitude towards the product was more positive than most medical employees, perhaps because of lack of staff training on the anticipated benefits. However, the interviewed patients would reduce the sweetness (somebody suggested the addition of lemon juice), and would like to change the consistence into something "more liquid", or "into the form of a biscuit" or powder. Rarer comments mentioned included suggestions for improving the packaging, such as "the sachet packaging should be replaced with ice-cream cup with lid".

3.6.2 Factors related to programme design

Certain problems in accessing and consuming the therapeutic food were accentuated by the design of the overall programme and inappropriate staff training.

Patients were not informed about how to correctly consume the RUTF. For example, counselling messages inappropriately advised adding the RUTF to tea, and feeding strategies that were not feasible for the patient. Suggesting to eat RUTF at meal times (three times per day), and/or together with ART drugs was not conducive to ensuring adequate intake. Some of the patients admitted that they disregard such advices because of the "strong" – difficult to eat - nature of the product, their bad clinical conditions combined with ART side effects (lack of appetite, nausea, vomiting, etc.).

More appropriate advice would have been based on therapeutic feeding guidelines [97] and have recommended small bites of RUTF throughout the day until the twenty-four hours prescription of sachets had been consumed. Box 1 presents the most common questions expressed by patients during this study. In the followup of this study, the same questions were used to lead to improved key counselling messages.

Frail patients who came to a clinic appointment without a carer sometimes ended up losing half of the prescribed RUTF supply as they were unable to transport the food to their home. The situation could be improved by redesign of the distribution system, perhaps involving community based organisations to support home-based care. Their importance is recognized in many HIV and nutrition interventions and protocols [244–248]. The health programme also needed to acknowledge and address the stigma-factor attached to Plumpy'nut®. This could involve the use of anonymous packaging.

In case of extremely frail patients, the carer played a fundamental role in trying to overcome key barriers for adherence like just opening the sachets or mixing it with other foods.

Both groups of adherence determinants identified in this study suffered from some limitations, described in the following section.

Box 4

During dietetic counselling sessions, the topics to be covered should respond to the following questions expressed by patients during the study: What is Plumpy'nut® (food/drug; composition)? Who is supposed to use it? What are its components? How often should I eat it along the day? What should I do when I do not manage to eat it because of nausea, vomiting or lack of appetite? Could I mix it with other foods? What should I avoid to drink or eat together with Plumpy'nut®? What are the consequences if I share my ration of Plumpy'nut® with other persons? Is it good for somebody who is not HIV positive to eat Plumpy'nut®? Is it good for somebody who is not thin to eat Plumpy'nut®? When should I stop eating Plumpy'nut®? Will I become thin again when I stop eating it?

3.6.3 Limitations of this study

This research did not correlate the collected data with clinical information such as patients' survival, CD4 count, weight gain or BMI changes which might have helped in understanding the impact of such programme in presence of household/community sharing, food mixing, lack of counselling, and clinical difficulties in swallowing among others. The access to the clinical information was not granted by MSF and the MoH, because of confidentiality-related reasons.

Reduced swallowing capacity was reported by study participants and directly observed. However, the research protocol had not foreseen to assess this aspect, and therefore only limited information could be collected.

The data analysis was done manually. The same analysis could have been peformed with the aid of a specialized software. However, at the time of the development of the research protocol (2007), such tool did not seem to be priority. That was in view of the only systematic review study available at that time, aiming at a mimimum criterion list for reporting qualitative research [242], and which found that only two out of twenty-two papers had reported the use of this kind of software.

Other limitations are related to the HIV therapy and the study setting. This research did not aim to understand the link between nutritional therapy and ART adherence. Moreover, RUTF are meant to be used in out-patient programmes, but this study was restrained by lack of observations at community level. In both cases, these information may have enriched the interpretation of the collected results.

The two study interpreters were not only employed as health promoters in the MoH HIV programme, but also HIV/TB patients in the same intervention. One of them had been previously successfully rehabilitated in the nutritional programme. Therefore, they might have previously met some of the patients enrolled in the study, and/or developed specific perceptions about the topic, introducing possible biases.

3.7 Conclusions

Overall, the research suggests that training and information material is needed to ensure that medical staff can support the patient to overcome the first most crucial phase of the treatment. The very first contact with the patient should include a test to assess swallowing capacity.

Reduced capacity to swallow is common and it may imply a lower adherence with nutritional therapy and an increase in mortality risk. Consistent with the community-based management of malnutrition approach [55,97] medical staff should ask the patient to eat some RUTF in their presence to verify her/his swallowing capacity. According to the results of this test, dietetic solutions must be discussed, agreed together with the patient, and the carer when present. Patients who are not able to swallow at all should be hospitalized and treated according to the in-patient nutritional therapeutic protocol developed by WHO [70] which utilises milk based liquid therapeutic nutritional products, such as F75 and F100.

The study showed that the Plumpy'nut®, designed for malnourished children, needs improvement to meet the palatability preferences expressed by adult patients. Reduction of perception of sweetness and fat components was requested by the patients. However, HIV/TB therapeutic nutrition programmes should not introduce newly designed RUTFs until positive clinical results have been demonstrated.

Further studies more closely correlating adherence and recovery rates are likely to improve the medical staff perception about the effectiveness of this kind of programmes, possibly improving their performance as well.

4 Designing the RUF formulation (sub-study 2)

In this chapter I describe a method to design an improved RUF formulation, minimizing its cost while fulfilling food-related standards and the international macronutrient requirements for this kind of products.

The method is based on a mathematical algorithm called Linear Programming. Its general features are described and contextualized, in the sections called “Evolution of the use of Linear Programming”, and “Linear programming applied to nutrition”. Following the latter, other sections focus, in order, on the description of the method in mathematical terms, on the specific objectives of this sub-study, on the phases which composed the applied method, on the obtained results of this sub-study, on their discussion, and on the drawn conclusions.

4.1 Evolution of the use of Linear Programming

Linear Programming (LP), an algorithm useful for planning and decision making, has contributed to shaping the modern world.

The founders of this tool are generally regarded as George Dantzig, who devised the method in 1947, and John Von Neumann, who established its theory, that same year [249]. Dantzig called the theory behind LP “the maximisation of a linear function subject to linear inequality constraints”[249], and his motivation initially consisted of the need to solve complex planning problems in wartime operations, reducing the costs of the army, and increasing its efficiency on the battlefield. However, soon after, advanced developments of this method also supported decision-making in large-scale enterprises, at worldwide scale. Its applications are many, and described here as follows.

Nowadays, many industries use LP as a standard tool to allocate a finite set of resources in an optimal way. In most cases, cost minimization is the final goal of LP applications. Examples include airline crew scheduling, shipping or telecommunication networks, oil refining and blending, and stock and bond portfolio selections [250]. Linear Programming has become popular also in academic circles, for operations research and management scientists, numerical analysts, mathematicians, and economists, who have written a large number of papers on this method, its applications and its further developments.

It is, however, only today that LP is applied in small-scale companies, where its use allows minimizing costs, and maximising profits, within the available resources. This delay is due to the relatively recent advent of powerful personal computers [251,252]. As the inventor admitted, LP calculations are time consuming, and they were impossible without readily accessible computer technology [251].

The LP method was applied in nutrition, often to minimize costs, but not only. The following section describes in which ways researchers, practitioners, policy and decision-makers have employed LP in the areas of animal, first, and human nutrition, later.

4.2 Linear programming applied to nutrition

In 1945, the nobel prize-winner George Stigler posed the problem of cost minimization of a balanced diet [253], and soon after the animal nutrition industry started using the advantages offered by LP [251]. In livestock feeding this method offers a large number of advantages and applications. For instance, LP cuts costs in production of animal feeds [254], improving their formulations [255], and helping in the determination of their nutrient requirements [256]. Linear programming also helped in determining to what extent cow food intake is constrained by the maximum feeding time available each day, by the daily rumen processing capacity, by the sodium requirements, by the energy metabolism [257], and helped predict optimized animal diet choices [258].

In 1959, the first LP application to human nutrition was described by Smith *et al.* [259]. Since then, a wide variety of applications followed, ranging from optimized management of food supplies on national and global scales, to menu planning for specific groups of people [260]. In 1983, the first paper described how to use LP to develop a diet in poor countries from the southern regions of the world [260].

Two questions are often asked, when researchers apply LP to nutrition-related fields. These are:

I. Is it possible to design or to improve nutrition recommendations, interventions, or diets using a pre-set range of limitations (e.g. food availability, price, access, etc.)?

II. If this is possible, what is the lowest-cost solution or formulation?

The following sections describe examples of LP applications used to answer the two questions above.

WHO urges countries to promote improved feeding practices to ensure optimal health in adults, and ideal growth and development in children [261]. Linear programming contributed in refining the same WHO nutrition recommendations. For instance, in a Malawian population, LP evaluated and improved diets recommended for young children during the complementary feeding period, while applying the WHO guidelines, and looking at consumption patterns of local foods [252]. The conclusions of this study contributed to tailor more adequate nutrition interventions, during the hunger season in Malawi.

In another LP study [262], the same authors predicted the food choices that an individual from French low socio-economic groups would make to reduce his or her food budget, while retaining a diet as close as possible to the one in the average population. The study assumed that economic constraints may contribute to unhealthy food choices. Evidence was found that economic measures are needed to improve the nutritional quality of diets consumed by underprivileged groups of French society.

The therapeutic formula milk F100 is used as the standard therapy for SAM, according to WHO [70]. However, it was not clear if optimized combinations of local foods from poor countries could achieve the same nutrient density levels of F100. With this objective, Ferguson *et al.* [263] explored the feasibility of formulating diets based on foods from Ghana, Bangladesh, and Latin America. None of the food combinations based on LP-models achieved the F100 densities of vitamin E, Riboflavin, Thiamine, Niacin, Zinc, Calcium and Copper. Therefore, the study concluded that the clinical efficacy of food-based therapeutic diets used to treat SAM should be thoroughly tested before use.

Linear programming can contribute to develop food-based dietary guidelines, which are required to combat micronutrient deficiencies. With this purpose in mind, Ferguson *et al.* [264] developed a rigorous four phase approach to designing this type of guideline, and illustrated the approach for Malawian children.

In other two studies, LP helped in optimizing the diet of two populations. In Thailand, Anderson and Earle [260] used LP to achieve an ideal diet formulation to be at the least cost, to meet specific nutritional requirements, to avoid over-supply of certain nutrients. The LP model included the composition of 150 common Thai foods. In Malawi, Briend *et al.* [265] used LP to determine a lowest-cost, nutritionally adequate diet for children using locally available food.

A method called Nutrient Profiling ranks foods based on their nutrient contents, and identifies commodities with a quality which is considered nutritionally good for their price. In a LP study, this approach was validated by Maillot *et al.* [266] in a large French survey. In the first part of the study, the authors correlated intake data of foods with their nutrient composition and with their prices. In a second part, the LP models designed theoretical diets that fulfilled nutritional recommendations at a minimal cost. The models from the LP were in agreement with the nutrient profiling rankings, suggesting that the latter can help identify foods of good nutritional quality accounting for their price.

Food prices can be analysed by LP to assess the economic values of fortified food supplements. Food prices and nutrient contents are linearly related to food weight. Therefore, LP can estimate the effect of introducing a food supplement on the minimal cost, required to provide a nutritional adequate diet to a population group[267]. Aiming for nutrition adequacy, the same method also provides an estimate of the expenses saved by the same group when consuming the fortified item, and compare them to the sums spent by the donor, after the distribution of the food supplement [267].

Linear programming is a reliable tool to design feeding recommendations. In Indonesia, one study [268] aimed to assess the application of population-specific, food-based feeding recommendations, developed with LP, to combat micronutrient deficiencies. The LP model was compared with another way to define requirements, which used data from both a cross-sectional dietary survey among infants living in a poor town district, and a food survey in three local markets. Results from both approaches agreed that theoretical micronutrient requirements could not be achieved using local food sources, and suggested that LP may be a reliable, and less resource-intensive method for this type of study.

Despite its potential, most of the acquired knowledge in LP applied to nutrition often

remains limited to the research realm. Briend *et al.* suggests that "its application into human nutrition practice is long overdue" [251]. That is true if considering the solutions for complex calculations, offered by relatively affordable computers of the current times. This aspect will be further described in the following section called "Software to apply linear programming".

Briend *et al.* [265] attributes one of the main reasons of this delay to the "complexity of mathematically modelling the underlying structure of food selection practices" and choices in human beings. It could be argued, that the same may be simpler in the feeding industry for animals.

In the next section, I introduce how the LP method and its components can contribute to minimize the cost of a diet, of a food, and more specifically of a RUF formulation.

4.3 The linear programming method

4.4 The main elements in linear programming

In mathematical terms, linear programming is "a tool to optimize (minimize or maximize) a linear function of a set of decision variables while respecting multiple linear *constraints*" [269]. In LP, the linear function is called the *objective function* (OF).

When used for selecting the lowest cost diet/formulation, the *objective function* can be expressed in the following form [252]:

$$Y = k_0 + k_1W_1 + k_2W_2 + \ldots + k_nW_n \qquad (A)$$

where Y is the cost, k_1, k_2… k_n are constants, equivalent, for instance, to the cost per unit weight for food ingredients F_1 to F_n, and W_1, W_2,…W_n are the *decision variables* (DV), i.e. the weights of foods F_1, F_2…F_n in grams.

The usual aim will be to minimize the cost of the formulation (Y) by changing the weight of the different ingredients while, at the same time, meeting a range of different *constraints*.

These mathematical constraints (equality, greater than, or less than) are imposed on one or

more of the DV (W_1, W_2,…W_n) to ensure that the nutrient content of the product meets design requirements and does not exceed upper thresholds.

Constraints in food formulation problems may be linear or non-linear but LP can only be applied when all the constraints are *linear* [252]. A constraint is considered linear when it can be expressed in the following way:

$$k_1W_1 + k_2W_2 + \ldots + k_nW_n \quad \geq a_0 \quad \text{or} \qquad \text{(B)}$$

$$k_1W_1 + k_2W_2 + \ldots + k_nW_n \quad \leq b_0 \quad \text{or}$$

$$k_1W_1 + k_2W_2 + \ldots + k_nW_n \quad = c_0$$

where a_0, b_0, and c_0 are constants.

Models including *non-linear* constraints may have several solutions (*local optimums*) depending on the initial values, and cannot be solved using LP. In optimizing dietary models, imposing the acceptable *range of the ratio* between the energy contribution from protein and total energy is an example of a non-linear constraint. If not too complex, non-linear constraints can be linearized, using mathematical transformations. The latter method will be described in detail in the methods section (see "Linearization of non-linear constraints").

4.4.1 Types of constraints

In LP, the constraints are important because the applicability of the models depends on the validity of the introduced constraints [262].

For instance, nutritient constraints aim to ensure that optimized diets or foods meet the nutritional needs of most people in the population [252]. This type of constraint defines the acceptable ranges of energy, protein, lipid, carbohydrate or micronutrients.

Nutrient constraints are common in published studies. For instance, several constraints of this kind were used by Briend *et al.* [269] to predict nutrients that are potentially low in child's diet, whereas Ferguson *et al.* [264] defined the constraints based on the recommended nutrients intakes.

However, some authors [267] warn that if only nutritional constraints are used, "LP can lead to unrealistic diets", "which may not be eaten in practice". To avoid this problem, constraints addressing palatability, texture and portion size may need to be introduced into the model [267]. This approach was applied for the first time in 1959 by Smith [259], and became common in the following studies, which included among others, constraints for the consumption of different food groups [252]. The choice of food group and portion size ranges should be based on previous food consumption surveys [265].

In summary, based on the available literature, nutrient-, palatability-, texture- and portion size-related constraints were identified as being useful in the design of realistic diets.

4.4.2 Constraints and unfeasible models

A LP solution is *feasible* when all its constraints are achievable in combination. When the highest possible concentration of a nutrient is less than a minimum constraint, or when the lowest concentration of a nutrient is higher than a maximum constraint, or an equality constraint cannot be respected, the model is considered *unfeasible* [263,264].

Models which are non-optimal may be reformulated, based on informed decisions from Sensitivity Analysis, which, using LP jargon, measures the strength of the different constraints. More precisely, the Sensitivity Analysis quantifies how much ingredient costs and formulation constraints can vary without requiring a change in the values of the LP decision variables and constraints. The Sensitivity Analysis function is available as part of some of the LP software described in the following section.

4.4.3 Software to apply linear programming

"Even for an expert, it is impossible to use intuition and guessing alone to arrive at solutions to problems which require solving hundreds of equations simultaneously" [251]. For this reason, nowadays, computer software identifying optimized LP models are available. Some authors [265,267] reported the following software to be of common use:

(a) Nutrisurvey (available on http://www.nutrisurvey.net/) is ideal for field-work purposes, user-friendly, but not flexible in terms of functions;

(b) Microdiet (available from Salford University since 1990) was designed to prescribe personalized diets in clinical settings or institutional practice;

(c) Microsoft Excel software (version 2007) comes with the Solver add-in that includes LP-based functions, (including Sensitivity Analysis), that some authors[251,265] describe as “user-friendly”.

4.4.4 Food composition databases

The validity of the LP-optimized formulations relies also on the accuracy of the nutrient data from the food composition dataset (FCD) in use, whose main elements consist of (i) a list of foods, and (ii) their nutrient contents.

When comparing two or more FCD, the way both foods and their nutrients are defined can be confusing. For this reason, the preparation of reliable data on food requires a precise nomenclature, a detailed description of the commodities, and accurate validated protocols to estimate their nutrient contents [270].

The process of finding international consensus on these aspects has taken time. In February 1947, the Committee on Calorie Conversion Factors and Food Composition Tables was convened by FAO, and only in 1989 did the FAO service INFOODS published the first set of food identifiers, also called “tag-names”. Since then, tag-names in FCD have constantly been updated [271] and organized in at least four systems:

- The *food classification systems* are specific for nations (or regions), whose identifiers are based on national criteria and whose food groups may be highly specific [272];
- The *Codex Alimentarius Food Standards* are prepared by the FAO and WHO Codex Alimentarius Commission, in order to protect the health of the consumer and to facilitate international trade in foods [272];
- The *CIAA Food Categorization System* is approved by the European Commission, and developed by the Confederation of the Food and Drink Industries of the European Union [272];
- The *Harmonized Commodity Description and Coding System* is prepared by the WTO, and used to generate global trade statistics.

Some studies[263,265] applying the LP-based method found that some of the tag-names from the available FCD were only partially matching the selected foods. In this case, the authors replaced the corresponding nutrient values with others from alternative FCD.

In most FCD, the nutrient contents are organized in tables. When available, technical notes come together with the tables, and describe the methods used to compile the datasets, their calculation processes, the units applied[271]. The notes are important in comparing food nutrients, coming from different databases. The variety of the methods and the calculation processes in use is large, and this makes the collation of composition data from national and regional datasets into global collections challenging. It is not surprising that most of the international FCD tables are expensive to compile, and, for this reason, the same collections are often only commercially available, rather than for free distribution.

The web site of the FAO INFOODS Secretariat (http://www.fao.org/infoods/tables_int_en.stm), however, reports at least fifteen international non commercial FCD tables, but most of them are dealing with specific food groups. These include foods important for biodiversity aspects (FCD released by INFOODS Food Composition Database for Biodiversity), sea food (Chemical and Nutritional Composition of Finfishes, Whales, Crustaceans, Molluscs and Their Products), staple crops (ILSI Crop Composition Database), and tropical foods (Tables of Representative Values of Foods Commonly Used in Tropical Countries) among others.

At least two studies [263,265] looking at LP-optimized diets used a FCD called World Food Dietary Assessment System (WFDAS) [273]. This is the base for the FAO food composition database called Minilist [273,274], and includes a list of 48 nutrients in 1,800 foods coming from six countries (Egypt, Kenya, Mexico, Senegal, India, and Indonesia) in four continents. Designed by the University of California, Berkeley, with funding from USAID, UNU and INFOODS, the program is in the public domain free distribution, and "generally accepted as being among the best"[275].

In Ghana, a RCT, which compared the growth in groups of children receiving micronutrient supplements, used the WFDAS collection [132]. Similarly, a FAO study [276] used the WFDAS to validate dietary diversity score as an indicator of nutrient adequacy for non-breastfeeding children .

The WFDAS offers an additional advantage. During human digestion, the phytate, which is contained in vegetal foods, limits the absorptions of key micronutrients, and for this reason it is necessary to quantify it. However, its content is often missing in most datasets, but not in WFDAS, which was, therefore used by Stein *et al.* [275] for this reason. In their study, these authors managed to analyze the health benefits of biofortification. It is not surprising that Gibson *et al.* [270], therefore, recommend the WFDAS dataset for most uses, and mostly for study related to low-income countries, where micronutrients deficiencies are common.

4.5 Why is linear programming important?

In nutrition, the reasons LP is important are many and two are the most cited. First, the LP-method is able to consider numerous factors, called constraints, guaranteeing that multiple desirable criteria, such as nutrient recommendations, are simultaneously met [264]. Secondly, LP can help to reduce diet operational costs[260].

In trialling diet recommendations or specific food specifications, LP replaces at least two more traditional methods, termed, by some authors[251], "trial and error approach" and "expert guessing". The first approach, an iterative method used to design diets, requires multiple backwards steps, and repeated diet designs to arrive at a solution that may or may not be optimal. Therefore, it is very resource intensive [269]. The other traditional method, based on more generic experts' advice, may instead suffer from a lower degree of rigour than LP [269].

In the management of undernutrition, LP is important, because has the potential to improve food-based formulations. For instance, the most common RUTF product is based on results from a limited number of studies, in a few settings, showing rapid weight gain [277]. Consequently, in other settings, with different underlying nutrient deficiencies and infectious disease profiles, similar weight gains would perhaps occur, with nutrient levels different from those in use [95,176,178,263]. Therefore, LP can efficiently identify improved combinations of RUTF ingredients that meet sets of improved specifications and these can subsequently be clinically tested.

Linear programming can decrease the cost of RUF spreads. As reported in section 1.3.3, improved lipid-based therapeutic, supplementary, and complementary foods are in

demand. However, their cost hampers scaling-up of nutrition programmes based on these products [40]. In RUF design, optimizing the combination of affordable, acceptable, locally available food ingredients, to meet endorsed nutritional requirements, represents an alternative option to be urgently developed.

Although LP offers evident advantages, no study was found testing a LP-based method for designing cheaper formulations of a RUF, which fulfils predefined macronutrient requirements, uses region-specific and culturally acceptable food, and that can be processed with locally available technologies.

For this reason, I undertook the study described in the following sections.

4.6 Objectives of the study

Aim:	Testing a method for optimal design of novel RUF formulations
Specific objective:	To design a cheaper RUF formulation that fulfils international macronutrient requirements and food-related standards
Research question:	How can linear programming based methods be used to design the cheapest formulation of a RUF that fulfils pre-defined macronutrients requirements, uses regionally-specific foods, which are culturally acceptable, and can be processed with locally available technologies?

4.7 Method

To explore the use of LP, I applied it in the process of formulating a RUTF prototype. After being manufactured from locally available commodities, the aim was that this formulation would be tested for use in adult therapeutic feeding programmes in East Africa.

In this study, the LP elements are the same described in the section “The linear programming method” at page 126 of this chapter. The OF consisted of identifying the

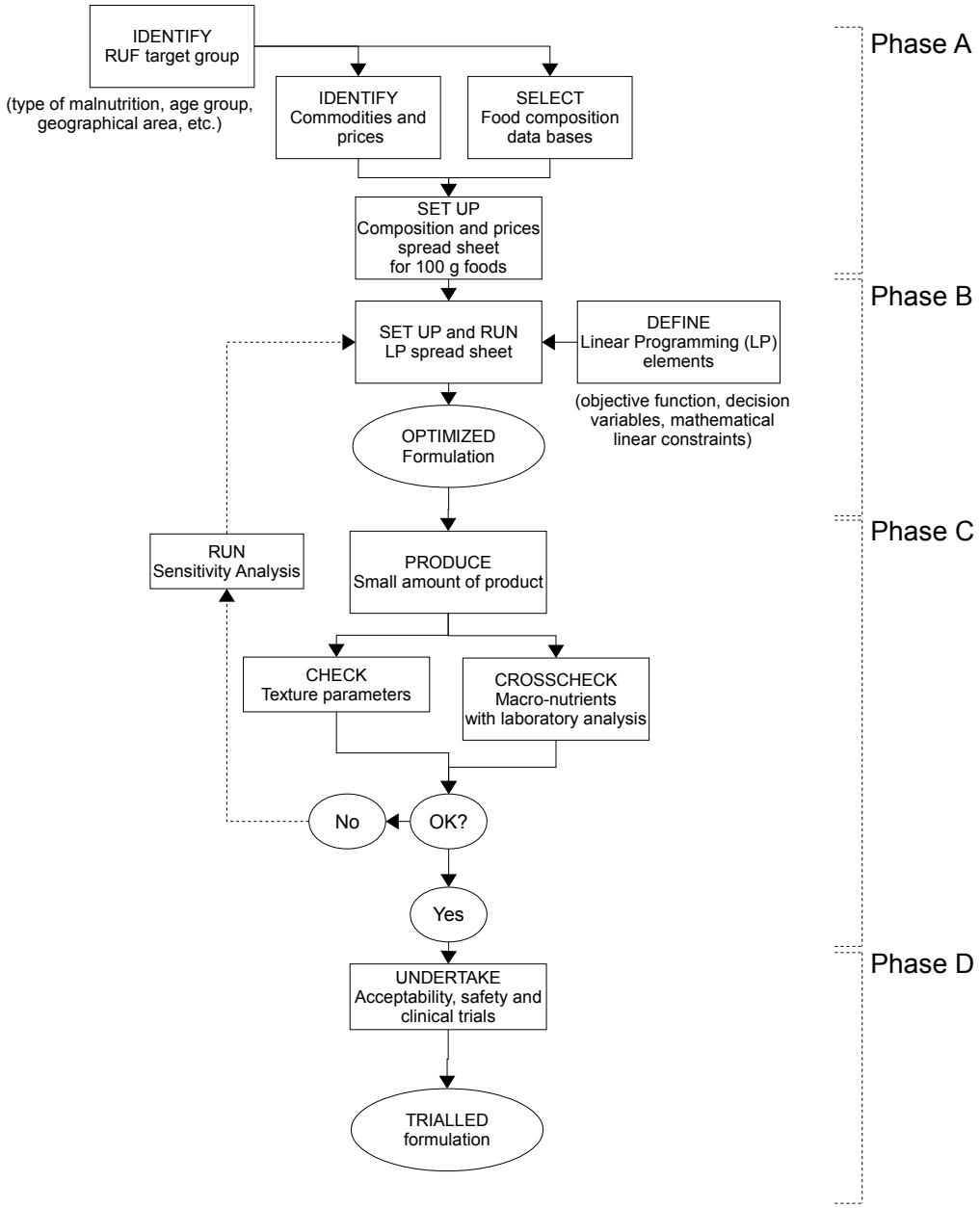
lowest price, which was given by the sum of each food ingredient cost, multiplied by the DV, while respecting the predefined constraints.

The overall formulation, which, overall, included design, manufacture, and testing of the RUTF, consisted of four separate phases (see Figure 17). The preliminary stage A involved defining the target group and the desired composition of the prototype product. Potential food ingredients, nutrient composition and price data were identified and compiled in this phase.

In step B, using Microsoft Excel (version 2007) and its Solver add-in function, I first defined and secondly applied the OF, the DV, and the constraints in order to set up and identify the LP-optimized model.

Phase C consisted of assessing the preliminary adequacy of the optimized model. First, a small scale test batch of the RUTF prototype was manufactured. Secondly, this allowed me to confirm that the desired texture was achieved, and to compare the LP-model macro-nutrient estimates with the laboratory-based results. In phase D, safety and acceptability tests were conducted with the unfortified product, and are described more in depth in subsequent chapters. Therefore, the following sections of this chapter focus mainly on Phase A, B and C.

Figure 17 - Proposed design and validation method for novel Ready-to-Use Foods.



4.7.1 Phase A: food composition databases and food prices

In this phase, I selected the FCD and identified the commodities to use in the RUTF formulation.

As introduced in previous sections, the validity of the LP optimized prototype formulation depends on the accuracy of the FCD. The following criteria, therefore, helped in selecting

their most adequate sources of compositional data:

- widest representation of commodity composition from around the world;
- largest number of nutrient data values per food;
- food descriptors matching the selected ingredients;
- dataset internationally respected, ideally including methods cited in peer-reviewed journals.

For the identification of the commodities, I relied on the Kenyan cereal/pulse blends processor Insta Products EPZ Ltd (Athi River, Nairobi), which, since the early 80s , has been the largest food aid producer in the region, supplying humanitarian organizations such as MSF, WFP, and the Kenyan MoH (Stuart Allison, private communication; 2008). Since, nutrition interventions across the entire East Africa currently distribute food products from Insta, at the time of this study, this manufacturer seemed a strategic choice for the potential production, at scale, of future RUF spreads.

In close consultation with Insta, I identified one commodity for each of four preselected food categories, namely (i) cereals (important for their carbohydrate contribution), (ii) pulses (for their protein content), (iii) sugar (contributing to the final taste of the product) and (iv) oil (high in energy density and crucial for the final texture of the product)

The choice of the *variety* of the cereal and the pulse had to satisfy general criteria that were agreed with Insta: cultural acceptability, high content of essential amino acids, and low price.

Based on the selected FCD, I compared the essential amino acid contents in the candidate cereals and pulses. Then I confirmed their cultural acceptability by verifying their presence on the traditional markets of the capital (Nairobi). Price data were provided by Insta, based on the past few years of their procurement records.

Representativeness of the food prices is important to achieve a realistically cheaper product. In view of this, Insta staff ensured that the food prices for the selected commodities were representative of an overall period lasting three to five years, accounting for the typical price seasonal fluctuations, and for the most common market types of

procurement (national or international).

4.7.2 Phase B: Setting up and running the linear programming model

In this study, the OF consisted of identifying the lowest price given by the sum of each food ingredient cost (C_1, C_2,…C_n), multiplied by the DV (food weights: W_1, W_2,…W_n), while respecting four groups of predefined constraints, derived from specifications for this class of product:

- energy and nutrient concentration;
- palatability;
- texture;
- total food ingredient weight.

The constraints and the LP model are described in the following sections and summarized in Table 13.

Energy and nutrient concentration constraints

Linear Programming constraints were introduced to ensure the RUTF formulation met the UN 2007 standards [55] for energy density, and the ratio of protein, fat, and essential fatty acids to energy (see values in Table 13).

Palatability-related constraints

Palatability constraints are common in dietary LP [265] and aim to avoid the creation of unacceptable tastes. In this thesis, the first sub-study, which was looking at compliance with the currently used paediatric RUTF. HIV/TB wasted Kenyan adults voiced the need for a reduction of the sugar content, which is equivalent to a value between 24 (personal communication: Briend, 2014) and 28 per cent according to two studies [278],[158].

Therefore, the per centage of sugar was constrained from 15 to 18 per cent (see Table 13), based on preliminary taste testing, although such small reductions in sugar may become challenging to be detected.

In small amounts, sorghum improves the taste of extruded pulse/cereal blends (personal communication: Stuart Allison, Insta Products EPZ Ltd; March 30th, 2008). We introduced a minimum constraint of 7 to 10 per cent for sorghum (see Table 13). The constraint range was based on preliminary work done with experimental formulations.

Texture-related constraints

Texture-related constraints aim for a specific consistency in the final food mix. RUF must have a paste-like property in order to be squeezed into the mouth by the wasted adult and children, or by their caregivers. Therefore, a fluid consistency was not suitable. A texture similar to a biscuit can produce choking in children [279], and therefore was also considered unacceptable.

A solid phase particle size below 200 microns [158] and a fat content ranging from 28 to 36 per cent generally led, during the preliminary tests, to a suitable paste texture. The latter criterion was included as a constraint in the LP model (see Table 13).

Total food ingredient weight constraint

Once the RUF is shown to be acceptable and safe (see Figure 17), a premix of vitamins and minerals is added to the formulation (Phase D). The weight of the food ingredients, therefore, needs to be constrained so as to allow sufficient space for inclusion of the vitamin and mineral fortificant in the finalized product.

A typical recipe for ready-to-use therapeutic food contains 1.6 per cent of premix[158]. However, estimations indicated that up to three per cent of the final product weight might be required for the premix. In agreement with the premix supplier, this per centage allows the inclusion of essential complementary components such as vitamin stabilizers and a micronutrient carrier, which consists of a refined starch powder (DSM, private communication; 2008).

I, therefore, used an equality constraint to fix the weight of the RUTF food ingredients at 97 g (see Table 13).

Table 13 Components of the LP model and prototype RUTF formulation

In 100 g of product	Initial Target Requirements	Optimized Solution
Objective function (cost minimization (*USD)):*	na.[1]	0.07
Decision variables: weights of the selected foods[2]:		
Soybeans, *g*	n.a.	31.9
Maize, *g*	n.a.	15.3
Sorghum, *g*	n.a.	7.0
Oil, *g*	n.a.	27.3
Sugar, *g*	n.a.	15.5
Constraints:		
Energy and nutrients		
Energy, *kcal/100 g*	520.1[3]-550.0	518.9
Protein energy/total energy[4], *%*	10.0 – 12.0	10.0
Fat energy/total energy[4], *%*	45.0 – 60.0	60.0
(n-3) Fatty acids energy/total energy[4], %	0.3 – 2.5	0.9
(n-6) Fatty acids energy/total energy[4], *%*	3.0 – 10.0	10.0
Palatability		
Sugar (sweetness), *g/100 g*	15.0-18.0[5]	15.5
Sorghum (taste improvement), *g/100 g*	7.0-10.0	7.0
Texture-related		
Fat content, *g/100 g*	28.0-36.0	34.6
Maximum food ingredient weight		
Final total weight, *g*	97.0	97.0
Monitored variables (not included as constraints):		
Quality of protein expressed as PDCAAS[6], *%*	75.0 – 89.0[7]	85.7
TFD[8], *%*	n.a.	83.0
Limiting amino-acid	n.a.	lysine

[1] The cost of the currently available product (Plumpy'nut®) is approximately 0.5 USD/100 g when delivered in East Africa, at the time of this study. The reference includes costs such as manufacturing, transport from Europe, packaging, and import taxes.

[2] Soy descriptor: soy flour full fat, raw (USDA SR20 [280]). Maize descriptor: maizemeal, wholegrain, white (FAO-Minilist [273]; item code CF00096). Sorghum descriptor: descriptor: sorghum, decorticated, flour (FAO-Minilist [273]; item code CF00154). Palm oil descriptor: Oil, vegetable, palm (USDA SR20 [280]). Sugar descriptor: sugar, white, cane or beetroot (FAO-Minilist [273]; item code SF00168) .

[3] The UN minimum specification is 520.1 kcal/100 g [55]. The constraint was relaxed to 518.9 kcal/100 g in order to achieve a feasible LP solution.

[4] The constraint formulae were converted to a linear form as described in the methods.

[5] The available literature [158] on paediatric RUTF reports a sugar content of 28 g/100 g. The constraint range was reduced to 15-18 g to make it more suitable for wasted adults living with HIV/TB (based on section 3.5 at page 108).

[6] PDCAAS: protein digestibility-corrected amino acid score [281].

[7] Calculation of PDCAAS based on [55,158,282] and using food composition data from [280,283].

[8] TFD: true faecal digestibility coefficient calculated using the following foods (and descriptors): maize (corn, extruded cereal), soy (soy flour), sorghum (sorghum, cooked) [281,284].

4.7.2.1 Linearization of non-linear constraints

In this study I transformed non-linear nutrient ratio constraints, such as the proportion of energy coming from protein, the proportion of energy coming from fat, and the proportion of energy coming from (n-3) and (n-6) fatty acids into equivalent linear constraints.

For example, the UN specifications[55] for RUTF require that the proportion of total energy (E) coming from protein is higher than 0.10 and lower than 0.12. This was expressed in the following non-linear form:

$$(P_1W_1 + P_2W_2 \ldots + P_nW_n) / (E_1W_1 + E_2W_2 \ldots + E_nW_n) \quad \geq 0.10 \quad \text{and} \quad \leq 0.12$$

where P_1, P_2,…P_n and E_1, E_2,…E_n represent, respectively, the energy content from protein and the total energy content (Kcal), in W_1, W_2,…W_n (g), of each food ingredient F_1, F_2…F_n.

Therefore, the protein:energy non-linear constraint was expressed as a linearized function of the weight of different foods:

$$W_1 (P_1 – 0.10\ E_1) + W_2 (P_2 – 0.10\ E_2) \ldots .W_n (P_n – 0.10\ E_n) \quad \geq 0$$

and

$$W_1 (P_1 – 0.12\ E_1) + W_2 (P_2 – 0.12\ E_2) \ldots .W_n (P_n – 0.12\ E_n) \quad \leq 0$$

Although LP can be quickly performed by a personal computer [267], some authors [265] suggest avoiding to linearize non-linear constraints wherever possible, because of the complexity entailed in the process. Therefore, I avoided including more complex non-linear/linearized constraints in the formulation, such as protein quality, expressed as Protein Digestibility-

Box 5 Protein Digestibility Amino Acid Score and True Protein Digestibility.

In human nutrition, for the measurement of the protein value of a food, FAO and WHO suggest the protein digestibility–corrected amino acid score (PDCAAS) method[281].

This is "based on comparison of the concentration of the first limiting essential amino acid (AA) in the (food) test protein with the concentration of that amino acid in a reference (scoring) pattern" or on the following formula:

$$\text{PDCAAS}(\%) = \frac{\text{mg of the limiting AA in 1 g of test protein} \times (\text{true faecal digestibility}(\%)) \times 100}{\text{mg of same AA in 1 g of reference protein}}$$

The score obtained is corrected for a true digestibility coefficient, which is specific for the food reference protein [284]. Based on the formulation provided by Manary[158], the PDCAAS value of the peanut- and milk powder-based RUTF is 85.7 per cent.

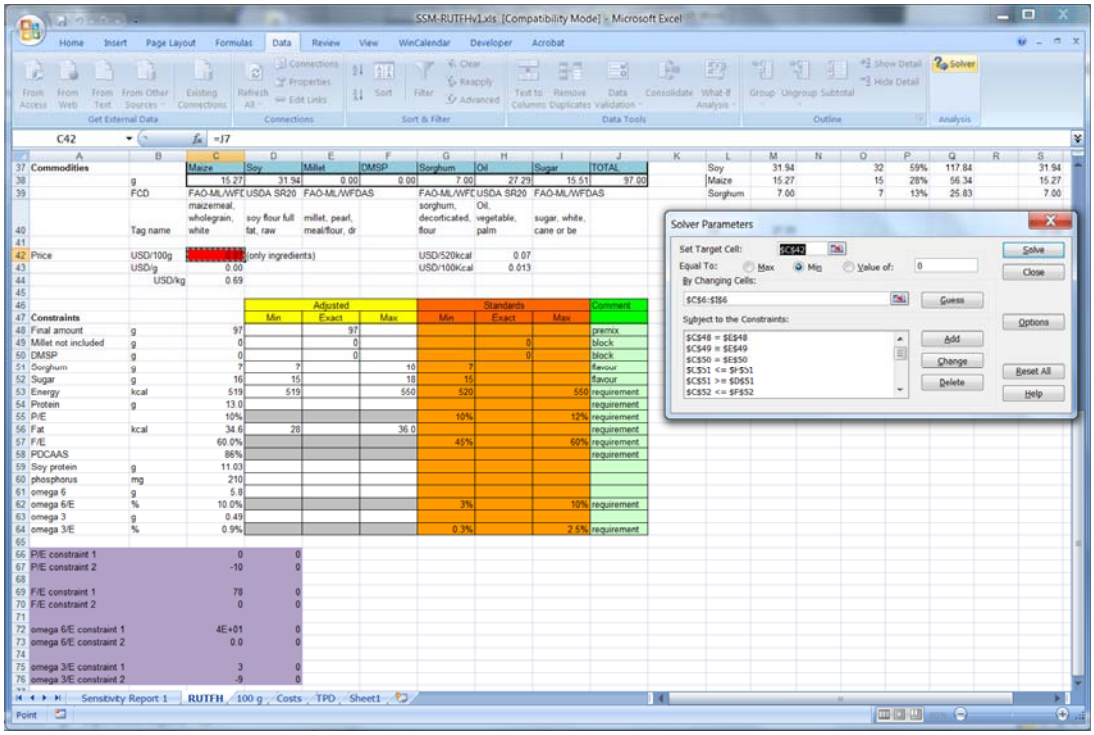
corrected Amino Acid Score (PDCAAS; see Box 5 for its description) [281], and true faecal digestibility (TFD; see Box 5 for its description) [284]. However, I calculated and manually assessed these two parameters in the final model.

4.7.2.2 Model optimization: the step sequence

In the process of running the LP model, I performed, in sequence, the following steps:

- creation of the data layout on a Microsoft Excel spreadsheet (see Figure 18);
- activation of add-in Solver Function (SF; see Figure 18), which is supplied with standard installations of Excel, as reported in previous sections;
- assignment of the OF, DV, and constraints described previously;
- activation of the Solver Function to identify the optimized LP model (see Figure 18);
- (if needed) activation of the Sensitivity Analysis function, which is supplied with the standard installation of the Microsoft Excel Solver add-in, as reported in section 4.4.3.

Figure 18 - Microsoft Excel Sheet to optimize RUF formulation using Linear Programming.



In the figure, the colours (if visible) are associated with elements which are part of the linear programming-based model: blue for the ingredients formulation, red for the "target" of the LP model (minimization of the final formulation price), yellow for the constraints applied in the model, orange for the standards to apply, purple for the linearized constraints and which, originally, were not-linear. The Microsoft add-in Solver function is visible in the window on the right side.

4.7.3 Phase C: comparison with laboratory results and sensitivity analysis

The Kenyan manufacturer (Insta Products EPZ Limited, Athi River, Nairobi) produced small batches of a RUTF prototype based on the LP-optimized formulation. A Kenyan laboratory (Polucon Services Limited, Msaada Avenue, Mombasa) performed the analysis (in triplicate) of the total energy, protein and fat content (see Table 15) in the prototype.

In this phase, I compared the lab-based results of the prototype against the LP-based estimates. I considered the model to be *acceptable* only if, in the two sets of data the difference in the relative energy density was below 10 per cent, and the difference in both protein and lipid densities were below 5 g/100 g. In food technology, these pre-stated difference values are cut-offs commonly used, although, they were not found described as such in the peer-reviewed literature.

To be acceptable, the prototype should also have been aligned with the considerations reported in the section “Texture-related constraints” (sub-chapter 4.7.2). Once data from the macro-nutrient comparison and the prototype texture were available, I considered the model acceptable, or not, based on an informed choice. In the algorithm of Figure 17, this step is represented by the symbol sequence “ok?”, “yes”, or ”no”.

If the LP-model was not *acceptable*, a re-formulation of the model was needed. With this purpose, first I performed a Sensitivity Analysis, with the SF add-in. The output of this function consists of a table reporting how much individual ingredient costs and formulation constraints can vary, without requiring a change in the values of the other LP decision variables or constraints. Secondly, I increased or decreased the constraints, within the interval suggested by the Sensitivity Analysis report, wherever possible achieving an *acceptable* model using the selected ingredients. In Figure 17, this step is symbolized by the dotted line.

4.7.4 Prototype production: consideration about its processing technology

When producing the prototype at Insta Ltd., I also considered food technology-related aspects. In food aid interventions, processed cereals and pulses for human consumption, involving no or limited cooking, must have a degree of starch gelatinization equivalent to or higher than 80 per cent (private communication; MSF Food Technologist, 2008), whereas their antinutritional factors must be non-existent.

Extrusion-based technologies may help in achieving these results. According to one large review study, the correct application of these processing techniques achieves levels of starch gelatinization sufficient for digestion [159] while destroying most antinutritional factors[159]. However, another study suggests that the overall digestibility does "not seem to substantially improve"[285] in presence of extrusion. This is so, because extrusion led, in this study, to a higher carbohydrate fermentation in the colon, presumably as a result of fiber solubilisation, with a possible suppressive effect on appetite. Moreover, this industrial method is available in most African capital cities, where also pre-extruding and milling operations can be commonly found. In view of these aspects, this technology was applied when producing the prototype.

4.8 Results

Based on the described method, I found that the improved RUF formulation, whose prototype reproduced a LP-based model, could be considered *acceptable*, modifying one of the pre-set criteria, and without the need to perform a Sensitivity Analysis.

Maize, soy, sorghum, palm olein oil, and sugar were the chosen commodities.

In the optimized solution, some energy and nutrient calculated values (protein energy/total energy; fat energy/total energy; (n-6) fatty acids energy/total energy) collided with the minimum or the maximum limits of the pre-set constraints.

Described in section 4.4.4, the WFDAS [273] was the ideal nutrient composition data source, since it fulfilled most of the pre-defined selection criteria. The WFDAS is based on data from six countries from East, West and North Africa, Central America, and South and South-east Asia. All these areas are affected by malnutrition, and therefore consistent with the goal of this study. However, essential (n-3) and (n-6) fatty acids were missing in the WFDAS. For these nutrients, I, therefore, used data from the USDA SR20 and Nutrisurvey databases[280,283].

Nutrients for maize, sorghum and sugar were obtained from WFDAS, and the *tag names* for these and the other commodities are available in the footnote in Table 13. Data for soy beans and palm olein oil were selected from another source, USDA SR20 (released in 2009), because their descriptors were closer to the commodities available. However, in this

dataset, soy figures for lysine and tryptophan were, respectively, 27 and 58 per cent higher than in WFDAS data.

The prices of maize, soy, sorghum, oil and sugar were respectively 0.3, 0.6, 0.3, 1.2 and 0.7 USD/Kg.

The final price of the formulation was 0.7 USD/kg. The initial minimum energy density constraint (520.1 kcal/100 g) was manually relaxed by only 0.2 per cent (518.9 kcal/100 g) in order to achieve a possible solution (see Table 13).

All the resulting ratios between energy from protein (0.10), from fat (0.60), from (n-3) and (n-6) fatty acids (0.009 and 0.10 respectively), and the total energy content matched the UN standards (see Table 13).

Expressed by the PDCAAS per centage, the quality of the protein (PDCAAS: 85.7 per cent; lysine was the limiting amino acid) was close to the upper level of the reference range (75-89 per cent). Part of the calculation of the PDCAAS, the True Faecal Digestibility coefficient (TFD) was 83.0 per cent. PDCAAS and TFD specifications are included in Table 13, whereas the process of estimating the PDCAAS and the TFD scores are described in Box 5.

Expressed as relative difference, the total energy in the LP model was 3.0 per cent lower than the lab-based figures. The protein and the lipid contents estimated with LP were respectively 2.3 and 1.0 g/100 g lower and higher than the contents measured in the sample (see Table 15).

Table 14 Sensitivity analysis of the final optimized model.

	Constraint	Allowable decrease	Allowable increase
Nutritional:			
Total energy, *kcal*	>518.9	1.24	0.03
	<550.0	31.0	<0.001
Protein energy/total energy	> 0.10	1.18	0.004
	< 0.12	10.38	<0.001
Fat energy/total energy	> 0.45	<0.001	77.85
	< 0.60	0.01	0.33
(n-3) Fatty acids energy/total energy	> 0.003	<0.001	2.87
	> 0.025	8.54	<0.001
(n-6) Fatty acids energy/total energy	> 0.03	<0.001	36.3
	< 0.10	0.003	<0.001
Palatability:			
Sugar level, *g*	>15	<0.001	0.50
	<18	2.4	<0.001
Sorghum, *g*	>7	0.87	0.02
	<10	<0.001	3.0
Texture:			
Fat level, *g*	>28	<0.001	6.6
	<36	1.4	<0.001
Maximum food ingredient weight:			
Final amount, *g*	=97	0.001	0.05

All the figures refer to 100 grams of product. Calculations were performed using Microsoft Excel (2007) with the *Solver* add-in function and the Sensitivity Analysis Report option.

Table 15 Comparison of the LP-optimized model and the laboratory composition analysis of the same formulation.

	Calculated Nutrient densities[1]	Laboratory results[2]	Absolute difference	Relative difference
	A	B	B - A = C	(C/A) x 100
Energy				
kcal/100, *g*	518.9	534.7	66.0	3.0
Protein				
g/100, *g*	13.0	15.3	2.3	17.7
Protein energy/total energy	0.10	0.11	0.01	-
Lipid				
g/100, *g*	34.6	33.6	-1.0	-2.9
Fat energy/total energy	0.60	0.56	-0.04	-

[1] Sources of food composition are [273,283].

[2] Methods applied (parameters, other information): Pearson (energy); Gafta May 91 (protein, Nx6.25%; lipid). By Polucon Services Limited, Msaada Avenue, Mombasa, Kenya; test report no. 2008/1282. Individual values for calculation of the variation were not available.

4.9 Discussion

In this study, I used the described method to successfully design a prototype RUTF product for the rehabilitation of HIV/TB wasted adults with SAM in East Africa.

Although today this method can be easily applied, historically, LP has received relatively little attention. This is so, perhaps, because computers were not widely available when LP was first conceptualized and disseminated[252]. The example illustrated in this chapter was implemented using software widely available (Microsoft Excel Office 2007 and its Solver add-in function).

In the optimized solution, three calculated energy and nutrient densities were exactly equivalent to the upper or lower limits from the pre-set constraints. This type of result is often observed when applying Linear Programming. As a consequence, criteria which *behave* in such a way become influential in the final optimized formulation. Therefore, in these cases, it may be relevant to compare the *calculated* values with the *real* values coming from the prototype. In my formulation, the energy from (n-6) fatty acids could not be tested, however, all the other calculated figures seem to match the prototype values, proving their robustness.

In the prototype formulation, laboratory analysis confirmed that the energy, protein, and lipid values were within the pre-established cut-offs (see Table 15). The relative difference in the energy density (3 per cent) was below the pre-set threshold (10 per cent), and the protein and lipid absolute differences (2.3 and 1.0 g/100 g respectively) were lower than the limit of 5 g/100 g. However, the relative difference in protein was large (17.7 per cent). This was not surprising, since it is known that protein content, in particular from cereals and pulses, can vary by a factor or two, depending on variety and fertilizer usage [286]. Except for protein, these results indirectly confirmed the relative accuracy of the FCD. However, food composition analysis (phase C in Figure 17), in particular for protein, remains a recommended step.

In this RUTF prototype, the subjective texture criteria (not too gritty, not too fluid), and the criteria for a sufficiently high PDCAAS were met. If the PDCAAS had not been close to the desired value, the limiting essential amino acid in the formulation, lysine in our case, could have been included as a constraint (Table 13), forcing the model to include a greater proportion of lysine-rich foods into the formulation.

In line with other LP studies in human nutrition [265], taste constraints were also introduced. The following sub-study assessed the preference towards this LP-optimized prototype. The results are presented in chapter 5.

It was not possible to meet the initial energy constraint. However, a global optimum model was successfully found by gradually relaxing the total energy constraint. Goal programming is an alternative method to LP, has been successfully applied to other dietary problems [260,261,268], and allows the model solution to have a range of OF, rather than a single one [259]. However, Goal Programming is more complex to apply. Since a solution could be found to the LP model by manually relaxing the energy constraint by only 0.2 per cent, we avoided using this more laborious method. In more complicated cases, a method based on Goal Programming may become more interesting than the approach described in this thesis.

In phase C (Figure 17) of the present study, adjustments to the formulation were not needed. However, in another models, the Sensitivity Analysis (data in Table 14) could be used to guide the analyst on how much each individual constraint could be varied without requiring a change in all the others.

In this study, the findings support the use of LP as a valuable tool to minimize the cost of a RUF formulation. According to UNICEF [119], sixty-eight per cent of Plumpy'nut®'s final overall price, excluding production and transport costs, consists of food ingredients. In Kenya, one kilogram of Plumpy'nut® costs approximately 5.00 USD (personal communication: Malik Allouna, MSF/France, Kenya mission; 2008). This suggests that the indicative price for the food ingredients component was 3.4 USD/kg at least for Plumpy'nut®. Therefore, the ingredient costs for the LP derived RUTF prototype formulation (approximately 0.70 USD/Kg) is likely to be substantially cheaper, even after the addition of the micronutrient premix[4]. Importantly, the lower transport and importation costs are also likely to result in a price advantage for locally produced RUTF. The regional agriculture economy may also benefit due to local purchase of the ingredients. However, more robust methods for economic assessment of RUF formulations are needed to support decision makers.

Future standard protocols for RUF design should address also other economic aspects, including validated methods to obtain food price data in low-income countries for use in LP models. In this study, it was challenging to find price data for ingredients, which well represented seasonal fluctuations at national or regional levels.

Some constraints were highlighted in applying LP to design food formulations of this kind. The accuracy of the novel RUF was highly dependent on the quality of the available FCD. Since the 1970's, researchers have realized that most foods exhibit variations in composition, and that a single table value cannot fully represent any particular food [286]. Nutrients figures must therefore be considered as estimates [286].

Section 4.4.4 describes the improvements proposed for FCD data collection and management. For example, INFOODS [271,274] and Codex Alimentarius web pages [287] report information on standardized nutrient analyses, and recent international protocols and software [288] trying to harmonize food tag-names. Despite these initiatives, no FCD source, used for this LP exercise, reported coefficients of variation or standard deviation figures, in spite of their use being internationally recommended [286]. Moreover, WFDAS showed some limitations. In this dataset, the same item descriptors were sometimes reported more than

[4] At the time of this thesis, the supplier had not communicated the final cost of the micronutrient premix.

once, or did not specify the food variety (e.g. in case of sorghum: white or red types).

In this study, lysine and tryptophan in soy beans data, retrieved from an American database [280], were higher than in merged non-American databases [273]. This might have overestimated the final RUTF protein quality. However, the Kenyan manufacturer reported that US soy beans were often present on the local market, and so may be used in products manufactured in East Africa.

The oil descriptor used, palm oil, was different from the actual used commodity, which was palm *olein* oil. Palm olein is an industrially prepared fraction of palm oil. Therefore, it can be speculated that its nutrient composition, mainly in terms of (n-3) and (n-6) fatty acids, are different. Unfortunately, the laboratory used in this study, and probably most industrial laboratories in Africa, are not equipped to measure (n-3) and (n-6) fatty acids. Rancidity of these nutrients is a major risk for the stability of food product with high fat content. Therefore, close monitoring of its shelf life is important.

Other important limitations of the chosen approach were related to difficulties in taking into account the presence of anti-nutritional factors in cereals and legumes. Michaelsen *et al.* [153] consider anti-nutritional factors "to have a negative impact on the solubility or digestibility of required nutrients and thereby reduce the amounts of bioavailable nutrients and available energy in the foods". These factors include (i) phytate and polyphenol compounds, which inhibit the absorption of proteins and minerals, like iron, zinc and calcium; (ii) alfa-amylase or protease inhibitors, which reduce respectively starch and protein digestion, (iii) phytohemagglutinins, which bind carbohydrate-containing molecules, (iv) saponins, which have negative effects on the permeability of the small intestinal mucosa, and (v) high content of soluble dietary fibers or alfa-galactosides, which may lead to flatulence. Therefore, these factors may contribute to reduce the nutritional rehabilitation of the beneficiaries of RUF's, or to prevent their growth or weight gain. For these reasons, the mathematical model should ideally include them, expressed as maximum level constraints. However, their actual contents in the foods was either unknown or expensive to estimate.

The designed formulation, which does not contain milk powder, may not be efficacious in rehabilitating children under five from severe acute malnutrition. This seems to be proved

but two randomized clinical trials undertaken while the finalzing the writing of this thesis. The first study, described by Oakley *et al.*[182], assessed malnutrition recovery in two cohorts of children, who received a RUTF with either a 10% or a 25% of milk powder. Recovery among children receiving 25 per cent milk RUTF was slightly greater than children receiving 10 per cent milk RUTF (84 per cent compared with 81 per cent after eight weeks; $P < 0.001$).

The second study, by Irena *et al.*[289] tested the formulation optimized in this chapter. This randomized controlled clinical trial assessed the recovery rates in two cohorts of children under five years of age, who received RUTF with either 25 per cent milk powder or the milk-free formulation. The recovery rates for SMS-RUTF and P-RUTF were 53.3 per cent and 60.8 per cent for the intention-to-treat (ITT) analysis and 77.9 per cent and 81.8 per cent for per protocol (PP) analyses, respectively. However, specifically in children with an age above 24 months of age, the recovery rate was equivalent in presence of both products.

The two studies suggest that nutrient components from milk in the RUF formulation play a role in management of acute malnutrition, at least in children under five years of age. Another hypothesis is that the antinutrient factors in the SMS-RUTF may have reduced the trial outcomes of both studies.

4.10 Conclusions

This paper describes a widely applicable method for the rational design of therapeutic food products at minimum cost. The study provided a prototype formulation, which met all the predefined requirements, except for one relaxed by 0.2 per cent, and also suggested, as a lesson learnt, the need for improved methods to determine the ingredient prices to use in the model.

The RUTF cost (based only on food ingredients) was approximately four to five folds cheaper than the current standard product (food ingredients and premix). Using the methods described here, public health nutritionists and food technologists could apply these steps to design other RUF formulations, such as ready-to-use supplementary or complementary foods.

However, the macronutrient content of LP prototypes always need to be confirmed by food composition analysis and the finalized products trialled under field conditions before they

can be recommended for general use [182,268]. This is true in particular in view of the fact that RUF formulations with similar macronutrient composition (e.g. protein quantity and quality), but different in food ingredients (e.g. dairy products replaced by combinations of pulses and cereals) may not lead to similar efficacy in rehabilitating from or preventing undernutrition.

5 Trialling the acceptability and the safety of a novel RUF formulation: a randomized controlled clinical crossover trial (sub-study 3)

5.1 Introduction

Ready-to-use foods must be both *acceptable* and *safe* in order to be efficacious. This chapter describes concepts of *acceptability* and *safety* and their determinants in health care and, most of all, in food science. It includes a brief review of the ways of measuring acceptability and safety, as described in the literature, and describes how these were applied to a case study. The last sections discuss the challenges in the interpretation of the collected data, while drawing conclusions which are useful for future similar studies.

5.2 Acceptability

Research looking into acceptability, both in health care or in food science, is relatively new, but an increase in the number of studies was noticed during the 1980's [290,291].

In 1981, Kadzin suggested that a health care treatment procedure is acceptable when "non professionals, lay persons, clients and other potential consumers" consider it "appropriate, fair and reasonable for the problem or the client", but also "non intrusive", and meeting "with conventional notions about what treatment should be"[292]. Currently, this is the most accepted definition[290,292,293] of health treatment acceptability.

In food science, disciplines such as dietetics, medicine, agriculture, social anthropology, sociology and psychology fuelled research exploring food acceptability [294]. However, Mc Ewan suggests that "there is no clear consensus as to what food acceptability actually is" [295]. That is confirmed by the current literature, where terms such as *preference* [295,296], *consumption* [297] or *acceptance* [298] were found inter-changeable meaning.

One general definition suggests that food *acceptability* measures the "interaction between an individual and food"[295], while another suggests that "the disposition of an individual to accept a particular food or drink, in particular circumstances, at a moment in time" is a more adequate way to describe the same concept[299]. However, in these and many other existing definitions, three components, namely physiology, attitudes and sensation, are common features [295], whose numerous determinants are crucial for understanding and interpreting food acceptability.

5.2.1 The determinants of acceptability

There is consensus that "the process by which man accepts or rejects foods is of a multi-dimensional nature" [300]. However, exploring the large literature available, most determinants of acceptability can be grouped into at least three categories: determinants related strictly to food characteristics, others highlighting the importance of the consumer's features, and a third group concerning the context where a food is consumed. The following sections explore these three categories of determinants, whose boundaries remain, however, imprecise.

The determinants of acceptability directly influenced by the food are many. These include the food's chemical and nutritional composition, including the role of chemosensory compounds [301], but also the environment in which the flavours are perceived [301]. Also, the physical structure and properties of foods[300], including their visual attributes such as light, fluid and thick appearance, creaminess, and flavour notes [300] are known to affect food acceptability. In some studies, the interaction of chemical senses with other oro-nasal sensation[301] and sweetness-related factors[302] are well described, whereas the hedonic-response to sweetness is known to be potentiated by the presence of fat components[302]. The latter clearly play a major role in determining acceptability, contributing to overall palatability[302], not only during chewing and swallowing [302], but also during digestion, with their activation capacity of satiety[303], which all increased or decreased the acceptability of foods in the available studies.

In studies looking at the monotony or the variety of food choices, within or across meals[303], over short (days, or weeks) or long periods of time (months or years)[303], diet diversity was found to be an important determinant of satiety feelings[303]. Menus, planned and previously communicated to the consumers, were found to influence food acceptability [303], as much as the food serving sizes[304], their combination of meal items[304], or the sensations produced by immediately prior events[301].

Culinary aspects studied in staple foods, such as their typical "processing techniques" and "characteristics of flavour combinations" [301], were determinants of acceptability as strong as the visual presentation, the label information and the package options related to the same food items [301].

Other determinants of acceptability seem to be related, instead, more directly to the food consumer. These include her/is gender[300,302,304], age[300,304], genetic[300,302], physiological[295,300,302], hunger/appetite conditions[295], or specific metabolic issues[302]. Among the latter, the literature reports that the food consumer is influenced by her/is overall nutritional status, and in particular by her/is body[302] and fat mass[302], as well as weight cycling[302].

In other studies, the level of education of the consumer[300], psychological factors[301], such as "the recall of pleasure"[301], and "the prediction of future feelings" [301] were found to be strong determinants. Others described in depth were potential behavioural issues such as eating disorders[302], abnormal "brain mechanisms" [302], but also beliefs, attitudes, food habits, radical opinions about food choices, perceptions of product safety [302], or "food appropriateness" to specific situations or the time of consumption [305].

Food acceptability determinants may have also a social dimension. For instance, the "effort" to obtain or the price of the chosen food[302] or social-cultural aspects related directly to the food choices[302], including their "convenience", their "prestige", the perception of nutritional added values[302], and the past or anticipated future events "that enter the mind of the subject at the time the reference event is occurring"[301] were found to strongly influence the way foods were considered acceptable.

Food acceptance cannot be understood without accounting for its context, as suggested by Rozin *et al.* [301]. This last group of determinants are related to the environment in which the food is consumed and/or socio-cultural factor attached to it. For instance, the way humans socially interact[304] affects food preference. That is true, at least, for the presence of family members, and when cultural habits, including religious elements[300] or features from naturally or artificially created groups[304] are present.

Urban and/or rural environments[302], or more generally the location of the consumption, may influence the acceptability of foods. For instance, the consumer reaction in a institutional setting, like a food-sensory analysis laboratory, is known to be often different from the one observed in a public place like a restaurant, or a private situation like a home or a kitchen [295,304,306]. Moreover the level of ability to make food choices, like, for instance, during a sensory test, or a convivial meeting proved to be a predictor of food

acceptability[306]. That is because of the presence, the absence and the degree of instructions to follow, which directly and significantly affect the measure of meal energy intake[306].

The determinants interact between themselves. But because of their large number, the way the described determinants affect each other is not entirely understood. However, few models have been proposed. For instance, Costell *et al.* [300] suggest that a consumer's response to a given food is mainly defined simultaneously by four intertwined elements. A *sensory component* is the first one which is described and correlated to the sensory properties of the product. Another is an *affective component*, responsible for positive or negative responses towards a product, whereas a *cognitive component* comes from the knowledge and opinions about the same food item. A *behavioural component* involves intentions or actions, defining how willing a consumer is to do something in a pre-defined situation. In other words, a food consumer never responds to an individual component input, but to all the inputs in combination, and is affected by the potential interactions between them [300]. The degree of each component input should be described by categories which are food-, consumer- and context-related[300].

The presented approach can, therefore, explain why taste preferences alone, for instance, do not necessarily predict food preferences and their related intakes[302]. This is so, although one review study[304] suggests that "meal and food choice continue to be the strongest factors that influences food perception and acceptability" [304].

In summary, the determinants of food acceptability are multidimensional and challenging to understand but their study is, nevertheless, important. This is because it can provide help in understanding eating disorders[306], and in measuring the acceptability of novel foods, "accurately and cheaply"[295]. The latter is relevant to my study, and described in the following sections.

5.2.2 Measurements of acceptability of foods

Depending on the subject under study, "different approaches, study designs and methodologies may be adopted to study food acceptability"[300]. The best way to measure acceptability of foods should be based on the determinants of interest, as described above. Because there are many, a large number of tools have been designed.

The most common are described in the following parts of this section, and included both qualitative and quantitative approaches, such as general questionnaires and interviews, food frequency questionnaires, food intake measurements, Likert-scale questionnaires, focus groups, consumers' diaries, blood chemistry samples, body weight, BMI and bowel function measures.

Knox *et al.* [294] opted for pre-validated questionnaires and interviews, which described diet histories and, therefore, assess the acceptability of a range of foods. However, these tools suffer from observer biases, due to the limited capacity of human memory, and its involuntary distortion of events [294]. Repeated 24-hour recalls are, therefore, often preferred [294] and complemented by in-depth interviews[300] in order to reduce this data collection-based problem.

Food frequency questionnaires are tools easy to administer, and, therefore, often used in food acceptability studies. Although inaccurate for the comparison of individual diets, these questionnaires remain valid when looking for the degree of acceptability existing among defined study groups[294].

Food intake measurements are common in many acceptability studies[294,302,303]. Intakes are expressed as the simple weight of intake, or, more accurately, as weight of intake per person body weight per time unit. However, these measurements can be resources demanding, time-intensive, and may alter the subjects' eating habits, distorting the interpretation of reality [294].

Likert-scales can be used to measure the degree of acceptability or rejection of health treatment[307], foods[302], or food supplements[308], but also their names, label design, appropriateness[305]. These methods are quick to administer, require minimal labour[305] and they come in different validated versions[292] with scales from 5 to 15 points. Their results should be expressed as the median score[308].

Focus groups involving facilitators, note-takers, audio-recorders, group dynamics, brain storming, non-verbal interactions between patients, food consumers, and/or caregivers, are often used to explore ideas, opinions and perceptions in acceptability studies [300,307], despite the fact that interpretation of their outputs can be labour intensive.

Consumers' diaries have been described as useful tools by some authors [294,295,306]. This is so, although the high degree of cooperation required from the participants means that sample attrition over the record-keeping can produce largely self-selected samples [294]. Moreover, self-report studies need to be validated by direct observational studies [306], often resource-demanding.

Physiological measures were largely employed in food acceptability studies. These included body weight, BMI measures[308], whereas blood biochemistry samples were often used to test the sensitivity and the sensibility of other research tools [308]. The median and interquartile range describing the functionality of the study participants' bowel were used to assess adverse events or general problems with adherence to dietary interventions and their controls[308].

The conclusions from food acceptability studies cannot be generalised to other populations, unless these have very similar socio-cultural backgrounds and/or physiological features [294]. For instance, children's, adults' and adolescents' food preferences require different models of interpretations. Children are often guided by taste alone, whereas, in contrast, food choices of adults tend to be influenced by nutritional beliefs and social attitudes [302], and surveys on adolescents' food habits suggest that food preferences are based on food-related attitudes rather than taste preferences, or beliefs[302].

Therefore, it is safe to argue that measuring true food acceptability is challenging. The most common research methods have focused on the evaluation of sensory-related aspects[306], rather than including social and cultural determinants. These are important determinants, but they often incur into measurement biases[295].

In summary, in studying food acceptability, some authors concluded that "from examining a single, simple, restricted, refined, experimental situation, it is impossible to comprehend either the variety or possible patterns of the variables controlling them"[306]. Therefore, only an adequate combination of the research methods and instruments described can be comprehensive enough to assess the acceptability of one, or more foods[307].

In my study, measuring the acceptability of ready-to-use foods presented challenges and

required solutions which differed from the assessment of their safety, which is described below.

5.3 Safety

Prior to being offered to malnourished individuals, ready-to-use foods must be proved to be safe. Throughout human history, the need for an adequate and safe supply of food has been a driving force for innovation in agriculture, food industry, and human culture in general [309]. For instance, the "development of food thermal processing" (or food bottling), which occurred at the end of the eighteenth century thanks to the contribution of Nicolas Appert[310], contributed to the victory of many Napoleon's wars. That was because, food bottling, under heat, increased the safety of the food supplies, improving the health and, therefore, the performance of his troops[310].

More recently, food safety became part of the institutional concerns of the modern society, at least in western countries. In 1908, the United States of America (US) Federal Food, Drug and Cosmetic Act prohibited additions of any toxic substance to food, and in 1976, the US Food Safety Council developed criteria for the evaluation of safety in food supplies and their ingredients. Since 1930, the Food and Drug Administration agency (FDA), in the US, , and since 2002, the European Food Security Agency (EFSA), , have been charged with ensuring the safety of the national food supplies.

According to Chassy *et al.* [309] "the situation is far different" in low economy countries. There, consumers and concerned institutions are more focused on "obtaining adequate food supplies and ensuring food security, than they are with food safety, although – paradoxically – their food is frequently contaminated with biological and chemical agents that have adverse effects on health" [309].

In today food risk analysis, a food is considered safe when we are reasonably certain that it will cause no harm if it is used as intended, under the anticipated conditions of consumption[311]. Because food safety is a Public Health prerequisite[312], it is also utterly important to be assessed, together with its determinants.

5.3.1 Determinants of food safety

The main determinants of food safety can be summarized in four categories.

a. Bacterial and viral pathogens - when present in consumed food, they can infect humans, causing illnesses[309];

b. Toxins - formed before and/or after food processing or cooking, they are produced by bacteria and fungi [309]. The latter, common in grains and nuts, are known to cause health issues as such as cancer, toxicity syndromes, gangrene, convulsions, and, in the long term, suppressions of the immune system[309];

c. Natural intoxicants – these are toxic molecules produced by plants as part of their defences[309]. An example of these substances is represented by the antinutritional factors found in legumes [309]. In the millenniums of human history, the process of crop domestication reduced the initial concentration of such toxicants;

d. Inadequate forms of semi-industrial / industrial processing, and home-based preparation of food (cooking) – these methods have the capacity to reduce to minimum the adverse effects from the determinants mentioned above[313], but only when applied correctly.

In summary, a food and its ingredients are considered *safe*, when their processing/preparation methods are correctly applied and, simultaneously, chemical and microbiological analysis confirm that their (a), (b), and (c) determinants are within acceptable ranges. The latter are pre-determined by public national and international institutions concerned with food borne diseases. However, in innovative foods, the methods and the principles used to confirm their safety are specific to this category of products[314], and are described in the following section.

5.3.2 The guiding principles to assess safety in novel foods

A food can be defined *novel*, when it has not been previously consumed by humans [309], and its safety assessment is always an essential part of its development[313]. For instance, since 2007, the European Food Safety Authority (EFSA) requires any food, which is novel in Europe, to undergo rigorous pre-market safety evaluations [315] in order to minimise the risk of food-borne diseases for consumers [315].

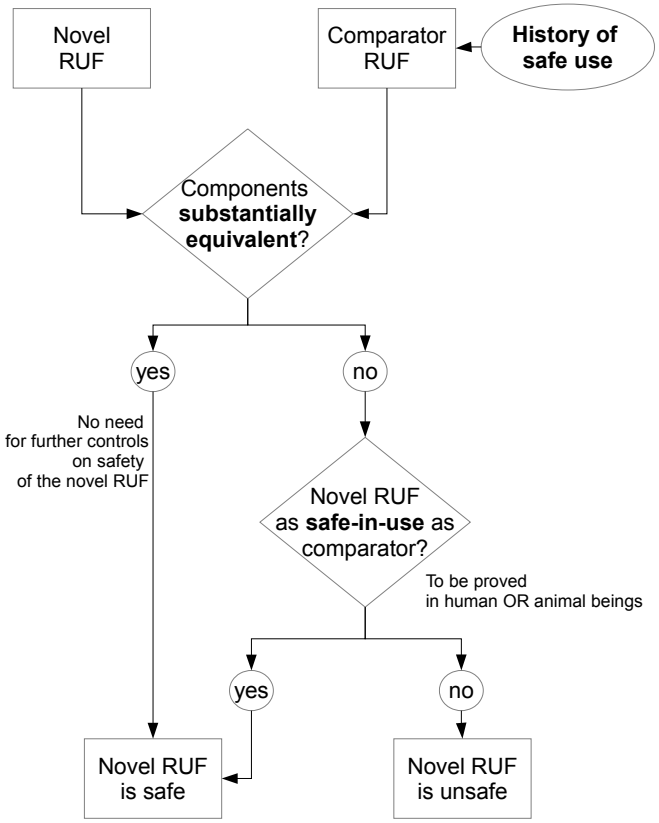
In a novel food, three guiding principles assess its safety based on comparison with a pre-

determined bench-mark product, called the "comparator"[313]. The principles are called "history of safe use", "substantial equivalence", and "safety-in-use", and are described in the following sub-chapter sections, and their sequence of use is showed in Figure 19. Whenever available, the control food is similar in many aspects to the innovative food, and must be proved to be safe by virtue of its established 'history of safe use' [313].

5.3.2.1 Principle "history of safe use"

Since the 1990s, the expression "history of safe use" is found in documents guiding the choice of comparator foods prepared by regulatory authorities (see Figure 19). This principle "forms the cornerstone of the safety evaluation of novel foods"[313]. However, in 2007, some authors[313] argued that existing criteria to consider a comparator "safe to use" should be improved.

Figure 19 - Algorithm to confirm the safety of a novel RUF



The text in bold indicates the application of one of the guiding principles supporting the testing of a novel food safety. Source: adjusted from the references [101,309,312,313,315,316].

For instance, a piece of evidence for considering a comparator safe is the documented absence of 'history of un-safety' [313]. This is defined, ideally, as lack of "robust and reliable, peer-reviewed, scientific publications, governmental documents and scientific expert opinions" suggesting cases of un-safety[313]. However, in reality, anecdotal evidence sometimes is the only information available[313]. Therefore, some comparators may be considered "safe in use", while in reality they are not.

Sometimes, no comparator with an acceptable 'history of safe use' may be found. In this case, the novel food is not necessarily unsafe, but requires complex assessment programmes[313]. These are not described here, because I identified a suitable comparator food, as described in the methods section of this chapter.

Whenever its "history of safe use" is documented, the comparator food assists the safety evaluation of the novel food, testing the existence of a "substantial equivalence" between the two products[313]. The concept supporting this approach is described more in depth in the following section.

5.3.2.2 Substantial equivalence between comparator and novel food

The "substantial equivalence" approach is meant to demonstrate any potential difference of safety risk between the comparator and the novel food (see Figure 19). The founding assumption is that food *components*, which are identical in the two products, pose the same level of risk[309]. Therefore, both in the comparator and the novel food, their *components* must be first characterised, and subsequently critically compared.

At least two types of components are generally considered. The typical *information components* include the food chemical and microbiological hazards, food preparation and processing, and the description of their consumer populations, whereas *component data* consist of the food moisture, protein, fat, amino and fatty acids, and micronutrient profiles, among others [313].

Based on this principle, only two cases are possible. If the components of both foods are identical, "substantial equivalence" between the novel food and its comparator is confirmed. Therefore, at least according to the European guidelines [315], novel foods demonstrated to be *substantially equivalent* to their comparators are to be considered safe, and no further safety assessment is required. However some authors[309] argue that this approach does not entirely eliminate the possibility that a novel food is unsafe, but it establishes only a "reasonable likelihood"[315].

In the second option, the comparison of the two component documentations fails to prove substantial equivalence between the novel food and its comparator. In view of this , any highlighted hazard needs to be further understood [315]. In the literature[315], the comparison of typical components involves verifying the existence of a certain level of risk of a lower

digestibility, a higher intolerance, and/or the presence of allergenicity in novel foods. If so, simultaneously in the novel food and its comparator, any of those risks must be clinically trialled by a study named "assessment of safety in use" [314] (see Figure 19).

5.3.2.3 Trialling safety-in-use

No endorsed protocol to plan trials to test safety-in-use in novel foods is currently available. However, the related scientific literature suggests which trial study design is at least ideal, and discusses when human participants, rather than animal, are needed.

The trials should include a control group. Moreover, a randomized allocation of the novel food and comparator among the study arms is recommended [312]. The number of the study groups should depend on the trial design, which is ideally factorial [316]. Few other study design features should be considered. These include: limiting the chance of both the observer and the participants knowing which intervention/control exposure they were allocated to[315]; statistical determination of the sample size for each study arm [312]; and data analysis controlling for the participants' anthropometry and overall diet[312].

Animal studies are cheaper, but often can not replace trials involving human beings[315]. This is because the generalisability of the study results from animals to humans is often limited. However, the EFSA [315] developed a guide, summarized here, suggesting when studies testing novel food safety-in-use may consider human study groups, taking into consideration at least three type of risks. These are: general safety, nutritional, and allergenic hazards.

In order to consider "generally safe" the involvement of human beings when testing novel foods for safety-in-use, EFSA recommends "a preliminary systematic review of the relevant existing information". In the study area of this doctorate, one recent systematic review [101] concludes that the home based therapeutic rehabilitation of SAM "appears to be safe"[5].

When planning safety-in-use trials, concerns about nutritional hazards may be raised. In this case, EFSA suggests to estimate the nutritional risk posed by hypothetical higher intake ranges of the novel food in the population of interest[315]. Effects from prolonged storage, excessive or incorrect processing and cooking should be also thoroughly discussed [315]. In

[5] In the study, safety was defined as low or no correlation with morbidities like diarrhoea, malaria and respiratory infections, and mortality.

our study, the macronutrient profile in the novel food meets the standard recommendations for RUF products [55] (see section 1.3.2.1). However, the choice of the technology (see section 1.3.2.2) to process the blend of pulses and cereals in the novel food tested in this doctorate may affect some nutritional aspects. For instance the digestibility of the starch or the absorption of some of the nutrients may be below the ideal levels..

When testing safety-in-use of novel foods, allergenic reactions may occur in association with one or more ingredients. However, in this case, EFSA recognizes that it is not possible to make an assessment without "testing in humans"[315]. Furthermore, based on the international code of Good Clinical practices, the need to assess a possible risk of allergenicity in humans must be also justified by the level of potential benefits [315]. In our study, peanuts are ingredients in the control product, although absent in the novel food. Peanut is a current public health concern, but no documentation was found suggesting adverse events due to potential allergenic reactions, neither in adults, nor in children who consumed RUF-control. This should not exclude the potential risk of allergenic reactions in such products.

In summary, the safety of a novel RUTF to be administered to wasted populations must be tested with a safety-in-use trial. The reason is that the "substantial equivalence" between the most common RUTF (based on the Plumpy'nut formulation) and the RUTF developed in chapter 4 cannot be shown. That is because of difference in their ingredients and the processing technologies employed for production.

Only seldom, humans should be part of studies testing food "safety in use"[312,317]. However, the risk of harm can be managed. In the improved RUTF formulation, potential highlighted hazards require closely monitoring of the study individuals' health condition, in order to ensure that they stop consuming the paste as soon as any adverse event may start to arise. On the other hand, the peanut- and milk powder-based RUTF is the ideal comparator of novel improved RUTF products. That is because its absence of documented adverse events remains unchallenged, both in wasted children and adults.
The importance of assessing and preventing potential adverse events in the early stages of human studies, could not be overemphasized. For this reason, after the definition of the study objectives, in the "safety in use" trial of the RUTF formulation optimized in chapter 4, the setting and the profile of the participants were cautiously chosen, as described below.

5.4 Objectives of the study

Aim:	Development of a method for trialling the acceptability and safety of a novel RUF formulation
Specific objective:	To compare the acceptability and the safety of a novel RUF with the most commonly used product, using a randomized controlled clinical crossover trial with HIV/TB patients in Kenya
Research question:	What are the lessons learnt in applying a method to compare acceptability and safety of a novel RUF with the most commonly used product?

5.5 Material and methods

The trial that I describe in this chapter tested, in wasted adults living with HIV and/or active TB, the acceptability and the safety of the RUTF formulation designed in chapter 4 against an ideal comparator food. Both products are described in the following section.

5.5.1 Trial and control products

The trial RUTF (produced by Valid Nutrition, Derry Duff, Ireland, at Insta Limited, Nairobi, Kenya) contained soybeans, maize and sorghum, no micronutrients premix, and is referred to here as SMS-RUTFh ("h" standing for adult HIV/TB). The control product (Plumpy'nut®, produced by Nutriset, Malaunay, France[318]) contained peanut butter, milk powder, a premix of vitamins and minerals, and is referred to here as P-RUTF. Both products contained sugar (24-28 and 15⁄100 g respectively for P-RUTF and SMS-RUTFh) and their macronutrients (energy, protein, lipids) closely met the UN requirements for RUTF as reported in chapter 1.3.2. Both their consistencies were paste-like, but their tastes and colours were different.

5.5.2 Study population

The study was carried out in two locations, two kilometres from each other, in Homa Bay town, Kenya. The participants, enrolled after written informed consent was provided, were patients recruited from the District hospital, supported by the Ministry of Health (MoH) and

Médecins Sans Frontières-France (MSF). The patients from the two study groups met each other only at enrolment (day one), and/or incidentally in the routine medical hospital visits.

The participants, HIV and/or TB infected, were considered eligible if receiving ART and/or TB treatment, their age was equal to or above 18 years, and their BMI was between 18 and 24 kg/m^2. According to the last criterion, the study group was not malnourished, and this aimed to minimize their risk of adverse events.

The exclusion criteria consisted of previous enrolment in a nutritional therapeutic programme, oral problems that prevented adequate swallowing (although typical AIDS oral thrush was not an exclusion criteria), and any specific food intolerance (e.g. peanut allergy). Subjects missing more than three days were considered defaulters.

5.5.3 Study design

The study design was a two-arm crossover randomized control trial. At enrolment the patients were given a number from 1 to 2, randomly generated using an Excel spreadsheet (*Rand* function), that corresponded to one of the trial groups. Each group received one of the two products during each phase, which was assigned to the participants following an AB/BA sequence.

Under direct observation, during two weeks (10 working days), water *ad libitum* and 250 grams of one of the two products were offered to the patients as a replacement of the midday meal, with the message “please eat as much as you wish”. An extra 50 grams was available upon request.

A maximum of two hours was allowed to consume the product, and no left-over could be taken away. After two weeks (phase 1), the study was interrupted for a seven day *washout period* and then resumed for two more weeks (phase 2).

The professional background of the research staff included nursing, nutrition, and counselling. None of them was working for the MoH or MSF, and they worked in a different study group each day, interviewing randomly assigned patients. The ratio of staff members versus patients was equivalent to 1 to 3. In-depth questionnaires and focus group guidelines were provided in both English and the local language (Dholuo), after being anonymously back-translated. The packaging concealed the product identification.

5.5.4 Study procedure and outcomes

In order to consider RUTFH acceptable and safe, it had to fulfil simultaneously the following criteria and sub-criteria for consumption, safety and preference.

5.5.4.1 Criterion 1: consumption

The consumption criterion consisted of three sub-criteria. The sub-criteria 'average consumption' was satisfied if average SMS-RUTFh intake was more than 75 per cent (187.5 g) of the offered amount within one hour (criterion 1.1; Table 18), whereas SMS-RUTFh 'daily consumption' was met if its intake was higher than 75 per cent of the offered food for more than 75 per cent of the days on the trial (criterion 1.2). Finally the 'comparative energy intake' criterion (1.3) was satisfied if the average energy intake per kg of body weight was significantly higher than 75 per cent of the energy intake from the P-RUTF.

5.5.4.2 Criterion 2: safety

Soy, maize, sorghum RUTFh was considered acceptable from the safety point of view if participants did not report any of five co-morbidity events more frequently than in the control product (criteria 2.1-2.5; Table 19). This parameter was expressed as the mean number of days in which morbidity events occurred during product consumption (10 days or less). Prior to the acceptability trial, microbiological testing of SMS-RUTFh was performed. The results were in conformity with the UN specifications for such products[55]. The choice of the most frequent co-morbidity events was based on a preliminary review of the available literature.

5.5.4.3 Criterion 3: preference

A product was considered preferred if its score was higher than the alternative in the following aspects: general preference, colour, taste, sweetness, and texture (criteria 3.1-3.5; Table 20). At the end of the trial, each participant was asked to select the most preferred product (criterion 3.6), and two focus groups were held to investigate participants' experiences and perceptions that other methods may not have captured.

5.5.4.4 Data collection

Quantitative data was collected daily and included: body weight, height and MUAC, weight of RUTF intake (Salter scale M021, max 500 ± 5g), 24-hour recall of nine clinical events, and individual eating duration. Body weight, MUAC and height were collected daily, weekly and at baseline, respectively. Individual interviews of all participants were held to evaluate the

preference for each product and used a 5-point Likert scale (with lower scores representing greater liking of a RUTF)[319].

Focus groups, 30 to 40 minutes long, used pre-selected lists of discussion themes, and the facilitators followed a written manual. Discussions undertaken in the local language were digitally recorded, transcribed into English, and twice a week, a diet diversity score (DDS) questionnaire (0-12 items type [320]) recorded the foods consumed at home.

5.5.4.5 Management of adverse events

Patients reporting any of the five clinical events for more than three consecutive days would have been immediately referred to the local clinic, and withdrawn from the study if the cause was considered to be related to RUTF intake.

5.5.5 Sample size

A paediatric acceptability crossover trial on RUTF [321] involved a sample size of thirty-one children, during two days of RUTF feeding, to detect a significant difference with alfa and beta errors of 0.05 and 0.95. Its power calculation, based on of RUTF daily intake, considered one standard deviation an acceptable difference to be detected.

However since previous research on RUTF acceptability was not available in adults, the nature of our study was exploratory. For this reason, when compared to the Indian paediatric study, the sample size (n=50 including drop outs) and the number of feeding days (10 repeated measures/RUTF/individual) were both increased, but limited by the available budget.

5.5.6 Statistical methods

Student's T test and regression models were used to test for differences between continuous data. The Wilcoxon rank-sum (Mann Whitney) test and sign test were used for non-normally distributed, un-paired, continuous data, whereas the Wilcoxon matched-pairs signed-rank test was used for non-normally distributed, paired continuous data, including the Likert scale 5-items score. The double-sided Fisher exact test was used to compare categorical data, and odds ratios and confidence intervals were calculated.

A linear regression model compared the energy intake of the two products after adjusting for potential confounders, including clinical events, socio-economic data and

anthropometry at enrolment. Logistic regression models explored if preference for a product could be influenced by group membership.

Analysis of ordinal score for preference criteria was based on logistic (not ordinal) regression, after regrouping the data into two categories (scores 1 and score 2, 3, 4 or 5 out of 5). This was because of the instability of the model, due to too few cases when cross tabulating outcomes and predictors.

When applicable, regression models benefitted from the robust standard error approach[322], so that the participant's series of repeated measurements were considered as individual clusters. Absence of carry over effect was checked prior to treatment-effect analysis, following a method described by Jones and Kenward[323].

Statistical comparisons were two-tailed, and all testing was conducted at alfa equivalent to 0.05, on per protocol data. EpiData version 3.1 software was used for data entry, and data analysis was undertaken using Stata IC version 10.

5.5.7 Ethical issues

This acceptability and safety trial were embedded into a larger research programme which had ethical approval granted by the Kenyan Medical Research Institute and National Ethical Review Committee (SSC No. 1414) to test the clinical effectiveness of SMS-RUTFh.

5.6 Results

5.6.1 Characteristics of the participants

On the 30th of June 2008, the study staff enrolled 51 patients into a five-week trial (see Figure 20). Two patients were excluded because they lived too far away. Twenty-four and 25 participants were randomly allocated into group 1 and 2 respectively. During the first phase of the trial, eight patients defaulted for more than three days, and were excluded. Two of them stopped coming after the second day of the trial for unknown reasons, and could not be traced. Six patients dropped out because of reasons not associated with products intake (transfer, other commitments). Forty-one patients successfully completed the study.

At admission, sex, marital status, BMI, and MUAC (Table 16) in the two groups were

statistically similar. The DDS did not highlight any statistical significant difference in terms of kinds of food intake at household level, between the two groups. No difference was detected between the two weeks DDS, nor within the same week for the same patients Table 17. No carry over regarding amount and daily energy intake was reported (*P*>0.05).

Table 16 - Characteristics of the participants at the start of the study (day 1), unless specified otherwise.

	Group	
	1 *(n=20)*	*2* *(n=21)*
Females, n (%)	*17 (85.0)*	*15 (71.4)*
Age,* years	*34 (29; 42)*	*30 (27; 35)*
Marital Status, n (%)		
Currently married	*10 (50.0)*	*12 (57.1)*
Never been married	*1 (5.0)*	*3 (14.3)*
Previously married and now widower	*9 (45.0)*	*6 (28.6)*
BMI at enrolment,* kg/m	*20.3 (18.9; 22.1)*	*19.9 (19.1; 21.8)*
MUAC at enrolment,* mm	*260 (229; 274)*	*266 (248; 280)*
Diet Diversity Score[†]	*7.5 (6.9; 8.2)*	*7.3 (6.7; 7.9)*
Participants who had tasted P-RUTF at least once before the trial, n (%)	*20 (100)*	*21 (100)*

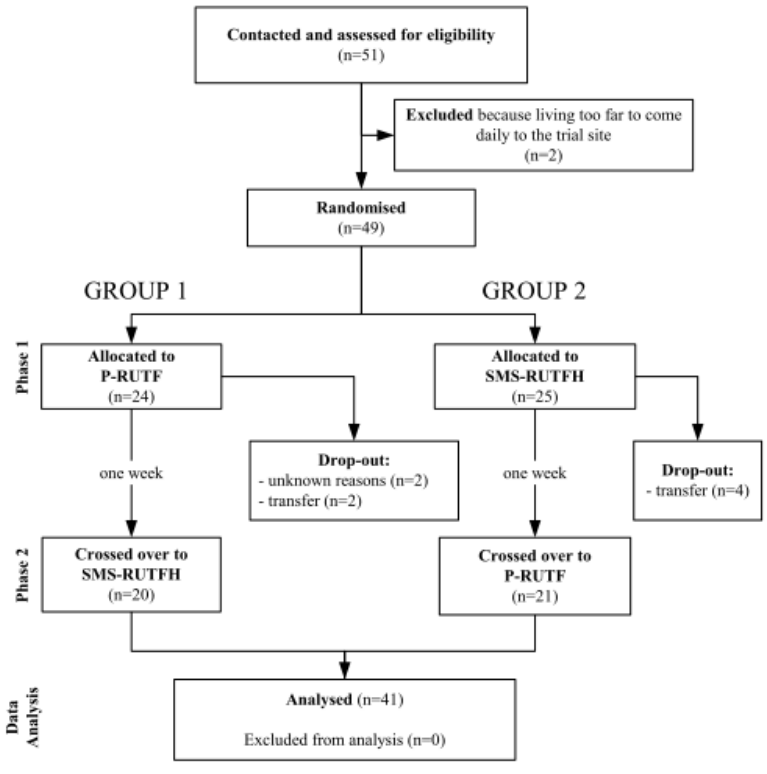
* Median and inter-quartile range (IQR).
[†] Medians and IQR of four measures over two weeks, two consecutive days per week (phase 2 of the trial).

Table 17 - Diet Diversity Score in phase 2 of the trial.

Week	*1*		*2*	
	Tuesday	*Thursday*	*Tuesday*	*Thursday*
Group 1 (n=19)	*7.4 (6.5; 8.2)*	*7.7 (6.9; 8.5)*	*7.4 (6.5; 8.3)*	*7.6 (7.0; 8.2)*
Group 2 (n=21)	*7.8 (7.1; 8.5)*	*6.7 (5.9; 7.6)*	*7.7 (6.8; 8.6)*	*6.9 (6.7; 7.7)*
Groups combined	*7.6 (7.1; 8.1)*	*7.2 (6.6; 7.8)*	*7.6 (6.9; 8.2)*	*7.2 (6.7; 7.7)*

The diversity score is expressed as mean (95% confidence intervals).

Figure 20- Flow-chart of the participants through the trial.



5.6.2 Measurement of acceptability

5.6.2.1 Measurement of consumption

Both average and daily consumption measurements were above the threshold (P<0.001; Table 18) for SMS-RUTFh, confirming that: all the patients consumed more than 75 per cent of SMS-RUTFh within an hour (criterion 1.1); that acceptable consumption occurred on more than 75 per cent of the trial days (criterion 1.2); and its energy intake was higher than 75 per cent of the P-RUTF intake in the two groups combined (P<0.001) (criterion 1.3).

A linear regression model (robust standard-error, 40-cluster analysis; R^2= 0.11; *P*=0.01; N=779) showed that the difference between the energy intakes of the two products (SMS-RUTFh and P-RUTF) was not statistically significant (*P*=0.06) when adjusted for confounders identified by a stepwise analysis (initial BMI, negatively correlated with energy intake, *P*=0.002; presence of throat sores, negatively correlated, P=0.13; 9 subjects out of 41 reported presence of throat sores).

Other potential confounders, which showed no or very small influence in the explored model and were not included, were age, and days of diarrhoea, nausea, and flatulence. However, the statistical power of the available sample size was likely to be relatively small.

5.6.2.2 Evaluation of possible morbidity effects

Most types of morbidity did not differ according to product consumption Table 19. Also, the average number of days with reported nausea and vomiting in participants consuming SMS-RUTFh was low (0.16 and 0.04 days of illness; 381 repeated daily measures).

However when applying robust standard error analysis, the data showed that these morbidities were significantly more frequent than when subjects were consuming P-RUTF (0.09 vs. 0.02; 398 repeated measures; P=0.04 and 0.03). Nausea or vomiting never occurred for more than three consecutive days.

5.6.2.3 Measurement of patient's preference

Results from the fortnightly interviews indicated higher scores for *general preference*, *taste* and *sweetness* for SMS-RUTFh (criterion 3.1, 3.3 and 3.4; P<0.001; Table 20), whereas no product was preferred in terms of *colour* (criterion 3.2). SMS-RUTFh *texture* was less preferred than the control (criterion 3.5; p=0.02).

At the end of the trial, the analysis of the combined sample (n=41) showed there was no difference in preference (criterion 3.6) between products (*P*=0.8). SMS-RUTFh and P-RUTF were preferred respectively by 52 per cent (95%CI: 36; 69) and 48 per cent (32; 64) of the participants. However, for most patients, the preferred product was the one allocated to them in the first phase of the trial. For participants starting phase 1 with product A, the odds to prefer product A were 5.4 times (95% CI, 1.4-20.4) higher than for participants starting product A in phase 2 (*P*=0.02).

The two focus groups organized on the last day supported the findings from the quantitative data and also suggested that "SMS-RUTFh texture needed to be refined", while "P-RUTF tasted salty" and "provoked more cases of flatulence". Moreover the patients were "not happy about changing the product from phase 1 to 2, once they had got accustomed to the first provided product", but felt that "the products were increasing weight" and physical "strength", and "reducing hunger feelings". No morbidity event was mentioned during the focus groups.

Table 18 - Product consumption in the two combined groups (N_1=20; N_2=21).

	*RUTF consumption**			P Value†	P Value‡
	SMS-RUTFh (n=381)	P-RUTF (n=398)	Threshold		
	A	B			
C1.1: Average consumption, g/d (95%CI)	232.5 (218.9; 246.1)	243.0 (230.9; 255.0)	187.5§	<0.001	<0.001
C1.2: Daily consumption¶, % (95%CI)	86.1 (78.8; 93.4)	87.7 (81.4; 94.0)	75.0	<0.001	<0.001
C1.3: Comparative energy intake: kcal intake/kg body wt/d (95%CI)	22.7 (19.5; 25.9)	24.5 (22.9; 26.0)	18.4 (17.2; 19.5)**	<0.001	<0.001

* Least square means and 95% confidence intervals.
† P value between SMS-RUTFh and threshold.
‡ P value between P-RUTF and threshold.
§ The threshold is 0.75 times the 250 g initially provided.
¶Per centage of days with consumption higher than 75% of the provided amount (250 g)
** The thresholds are 0.75 times the P-RUTF figures.

Table 19 - Safety criteria using 24-hour morbidity recall in combined groups (N_1=20; N_2=21).

Criteria	Number of days* during which morbidity events occurred		P value
	SMS-RUTFh (n=381)	P-RUTF (n-398)	
	A	B	
C2.1: Nausea	0.16 (0.05; 0.47)	0.09 (0.05; 0.14)	0.04
C2.2: Vomit	0.04 (0.01; 0.19)	0.02 (0.01; 0.04)	0.03
C2.3: Stomach pain	0.14 (0.05; 0.38)	0.16 (0.10; 0.25)	NS
C2.4: Flatulence	0.13 (0.05; 0.36)	0.16 (0.09; 0.26)	NS
C2.5: Diarrhoea	0.36 (0.03; 0.70)	0.31 (0.13; 0.49)	NS

*Least square mean and 95% confidence interval.
NS: non significant.

Table 20 - Criteria for food preference (Likert score type; 5-items) in the two groups (N_1=20; N_2=21), expressed on the last days of phase 1 and 2 of the trial.

Criteria		SMS-RUTFh* (n=39)	P-RUTF* (n=41)	P value
C3.1: General preference				
	Median (IQR)	1 (1;2)	2 (2; 3)	<0.001
	Mean (95%CI)	1.4 (1.2; 1.5)	2.4 (2.1; 2.8)	
C3.2: Colour				
	Median (IQR)	2 (1; 3)	2 (1; 3)	NS
	Mean (95%CI)	2.0 (1.6; 2.4)	2.1 (1.7; 2.4)	
C3.3: Taste				
	Median (IQR)	1 (1; 2)	3 (2; 4)	<0.001
	Mean (95%CI)	1.5 (1.3; 1.8)	2.7 (2.3; 3.1)	
C3.4: Sweetness				
	Median (IQR)	1 (1; 2)	3 (2; 4)	<0.001
	Mean (95%CI)	1.7 (1.3; 2.0)	2.3 (2.5; 3.3)	
C3.5: Texture				
	Median (IQR)	2 (1; 4)	2 (1; 2)	0.02
	Mean (95%CI)	2.3 (1.8; 2.7)	1.7 (1.4; 1.9)	

* The scores range was from 1 (very good) to 5 (very bad).
NS: non significant.

5.7 Discussion

The present study demonstrated that most pre-stated criteria for acceptability of a novel RUF were satisfied, confirmed the utility of the proposed method and, at the same time, illustrated lessons that will contribute to improving future trials of a similar kind.

5.7.1 The acceptability of SMS-RUTFh

The findings of this study suggest that, in this participant group, SMS-RUTFh intake was adequate, and it was preferred in some regards to the current standard product. The patients could consume most of the trial product provided throughout the study, exceeding the selected threshold for adequate energy intake based on the control RUTF.

In spite of the higher (8%) energy density of P-RUTF, the energy intakes of the two products were statistically similar when adjusted for possible confounders; but the study might be underpowered to highlight a difference. Among the identified confounders, it can be speculated that throat sores reduce the swallowing-capacity of the patients.

The qualitative study on the compliance of the use of P-RUTF, theme of chapter 3, achieved a similar conclusion. In SAM patients, cases of swallowing difficulty, need to be detected early by medical staff, and ideally addressed with appropriate in-patient care using therapeutic milk formulas (F75 and F100)[70]. As soon as the swallowing capacity is restored, generally in a few days, RUTF-based nutrition can be started and home-based care established.

The regression analysis found no evidence of increased morbidity associated with SMS-RUTFh consumption for most parameters. Although the frequencies of nausea and vomiting were higher in SMS-RUTFh than in the control product, they never affected participants for a prolonged period, and days of illness appeared to be randomly scattered along the time course of the trial. The regression models showed that the two co-morbidities were not associated with a decreased energy intake. This suggests that the cause(s) might be due to chance or unknown factors, but that these and other events need close monitoring during any future clinical trial.

The score for general preference was higher for SMS-RUTFh and its taste and sweetness were also preferred. However, its texture was less liked than P-RUTF, and this suggested the need for improved industrial processing to enhance the SMS-RUTFh consistency.

The order the RUTFs were offered to the participants was important. SMS-RUTFh consumption increased or decreased, according to whether it was provided as the first or second product. That might be because it was difficult for participants to adapt to a novel product once they are accustomed to the previous one.

Some constraints were highlighted. The participants of the trial were enrolled in the MoH/MSF HIV programme and had all been exposed to P-RUTF. Information of this kind, acquired prior to direct experience, could have shaped the food consumption and preferences as suggested by Costell *et al.* [300].

5.7.2 Lesson learnt about the method

This study highlighted important aspects in the application of methods to assess RUF acceptability. Among these, the results confirmed that a combination of both quantitative and qualitative measures is needed to capture the complex of factors influencing acceptability. The carry over effect analysis, recommended in crossover studies[324], showed that the wash-out period (one week) was adequate and might be reduced for future trials.

The sample size (n=41) compares favourably with an Indian study, whose sample size was powered for a difference of at least one standard deviation. Determining the equivalence or non-inferiority of SMS-RUTFh to the current standard product, rather than its statistical superiority to pre-stated thresholds, represents an alternative study design used to robustly validate a novel therapy [325], but requires a large sample size [326]. Other randomized trials [71,116,321], comparing RUTF with alternative food-based therapies, did not apply these methods. It is also important to note that the method described here is designed to be used in conducting an acceptability trial that precedes a RCT of clinical efficacy.

The study had some constraints. Ten days of RUTF intake, in each phase of our study, might have been too short to simulate the nutrition rehabilitation therapy in wasted adults (3 months; MSF/Kenya, personal communication, 2008). The main use of RUTF is in out-patient and exclusive feeding programmes. The study patients, instead, had access to the RUTF during only one daily meal, far from their households, while they were observed by

the research staff.

The SMS-RUTF did not contain the micronutrients premix, which might alter the final taste of the product and the findings of the trial. A taste comparison between RUTF with and without premix therefore must be carried out in order to confirm these acceptability results.

Aflatoxin is a global public health concern[327–329]. RUTF's containing peanuts in particular, but also other legumes and cereals, are potential carriers of this toxin. Therefore, they can increase the risk associated with morbidities. Safe limits of aflatoxin level intakes are still surrounded by a global debate. In spite, our study did not account for this health issue, creation of evidence in this area is in urgently needed.

5.8 Conclusion

There is no "gold standard" to test food acceptability. In spite of such a constraint, this exploratory study demonstrated the utility of this method and the acceptability of a novel, locally produced, RUTF. Its safety, mainly from the points of view of nausea and vomit, should be carefully monitored during the following clinical trial. Lessons about the method were learnt from the implementation of the study and they should contribute to improving future trials.

7 General discussion and implications

This research described an innovative method to design and pre-test improved and cost-effective RUF spreads, prior to subsequent clinical trialling. A case study was used to identify the strengths and the weaknesses of this method. This work was varied out with the overall goal of improving the performance of community-based, humanitarian feeding programmes.

As documented in the first part of this thesis, undernutrition, in all its sub-forms, is still a worldwide morbidity and mortality risk factor both for children[1] and for adults[45]. Its consequences, notably the physiological and psychological impairment of its victims, are often among the main causes of reduced survival. Eight decades of medical and nutrition research (section 1.2.1) has led to improved dietary solutions in low-resources settings, based on lipid-based, ready-to-use food products described in section 1.3. Section 1.4 detailed how the lack of a framework to design and validate improved and, potentially, cheaper formulations is currently limiting the global scale-up of their production and use, despite funding being available [40].

The method described in this thesis proposes an evidence-based framework for the pre-clinical product design and validation. The following sections discuss the key findings of the proposed new approach, highlight the potential implications for interested policy-makers, donors, public health practitioners, and food technologists, list areas for further research, and explores the limitations encountered.

7.1 Key findings

Based on the results reported and discussed in detail in the previous chapters, I describe here the main key findings observed in the application of the proposed method to the chosen study group. The study group consisted of adult patients, suffering from HIV wasting.

First, I tested a method to explore the adherence of the study group to the current nutrition rehabilitation therapy, and the key barriers to compliance. The application of the qualitative method, in a HIV programme in Kenya, found a low level of reported adherence to the prescribed dose of P-RUTF. Other important findings suggested that an improved approach to treating malnourished HIV-positive adults must consider strategies to support patients without a caregiver; that the current product (P-RUTF) must be more suited to adult taste;

that specific dietetic training for health staff is needed; and that liquid therapeutic foods (F75 and/or F100) must be provided to severely ill patients, unable to swallow.

Secondly, I tested a method to formulate and improve RUF products. The method, based on linear programming, formulated a RUTF which was three to five times cheaper than the current standard, based on locally processed foods (soy, maize, sorghum, among other ingredients), regionally available, and met local cultural and taste preferences of the study group. The formulation, called SMS-RUTFh, met also the macronutrient requirements in the rehabilitation of both wasted adults and children.

Subsequently, I tested a method to confirm the acceptability and the safety of the novel RUTF spread. A randomized, semi-blinded, controlled, crossover trial found that the SMS-RUTFh appears to be acceptable, and can be safely clinically trialled, if close monitoring of vomiting and nausea is included.

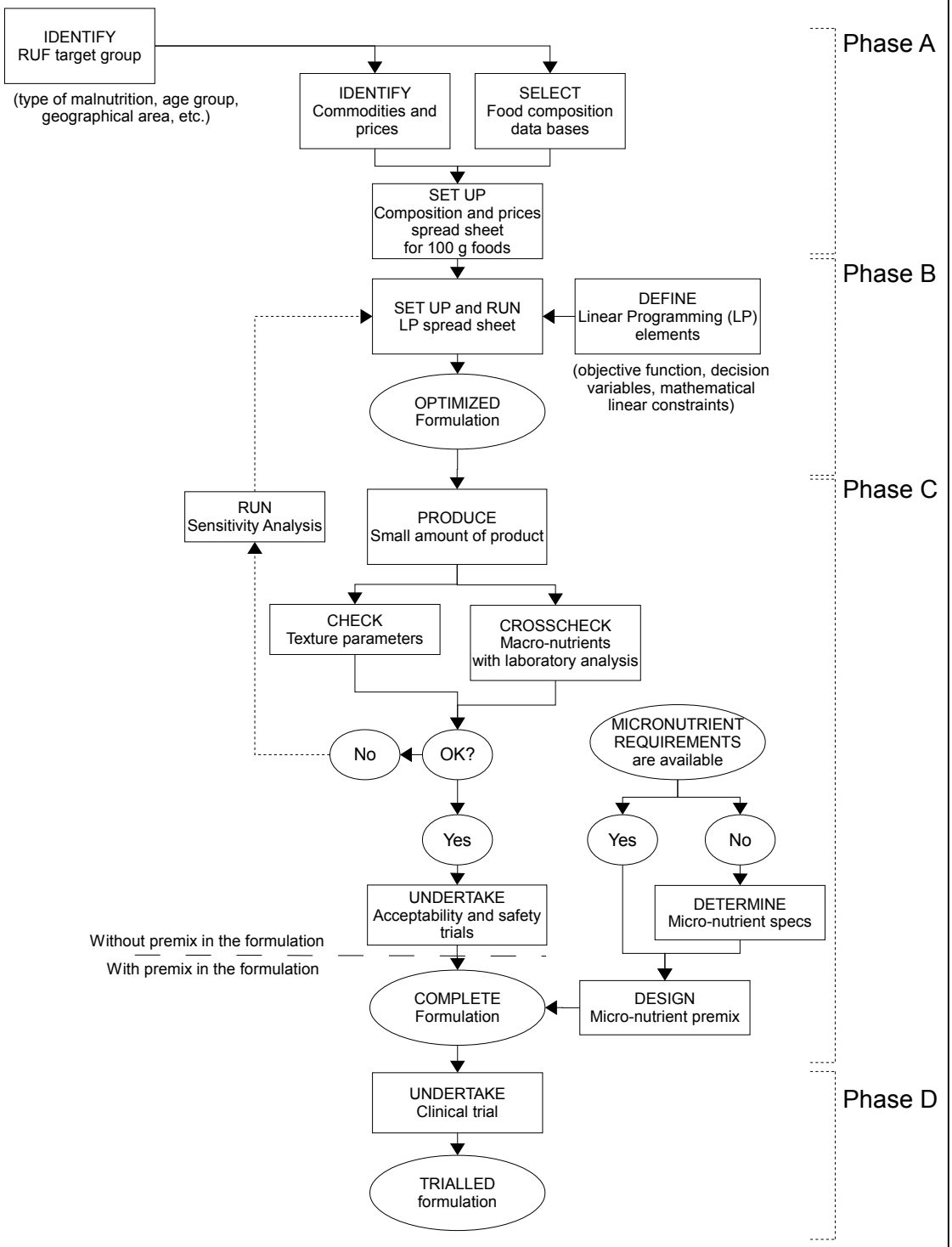
Lastly, micronutrient requirements for the treatment of HIV wasting in association with active TB are currently not available. Therefore, I developed an evidence based method to propose RUTF micronutrient specifications for the considered study group.

7.1.1 The framework

Based on the outcomes of my thesis, I developed a framework that summarizes the entire process to develop, pre-test and clinically trial novel RUF products. The clinical trialling is not part of the aim of this thesis. However, for reasons of completeness, it was included in the framework described in Figure 29. Furthermore, a complete clinical protocol was designed in collaboration with MSF/Netherlands to trial the RUF developed in my case study.

In my framework, the design and the pre-testing were organized in a sequence of three phases or process stages. The results of each phase formed the basis for the subsequent phase. In Figure 29, the outputs of phases A, B and C were respectively (i) the set-up of all the parameters to insert into the LP model, (ii) the optimized theoretical LP formulation, and (iii) a prototype tested for its acceptability and safety, which includes the micronutrient premix. The three phases were based on one, or more, sub-studies of this thesis, and they are described in the following sections.

Figure 29 –A design and validation framework for novel RUF.



7.1.1.1 Phase A

In stage A of the framework, the group to be rehabilitated by the RUF spread in a hypothetical nutrition intervention is defined. On these bases, the requirements of the improved product are then set.

Sub-study 1 proposed and tested a method to identify what improvements to the product may be required, from the perspective of the consumers. The same study also offered important insights into the barriers limiting RUF adherence from a programme-based point of view. However, the latter are intervention-specific, and therefore do not appear in the flow chart in Figure 29.

In phase A the potential food ingredients are identified, along with data on the macronutrient composition and price, which were compiled to set up the LP model. This operation is undertaken in phase B of the framework.

7.1.1.2 Phase B

The objective of phase B of the framework is the optimization of the RUF formulation. The method discussed in the sub-study 2 suggested one of the possible ways to pre-set the decision variables, the constraints, and the objective function in the LP model. Some of the LP constraints consist of the demands raised by the RUF users.

The optimal formulation identified by the LP model is theoretical. Its limitations were discussed in depth in sub-study 2. Its conclusions suggested that the quality of existing data for the macronutrient composition of the food ingredients may be inadequate. Therefore, comparing the estimated nutrients in the LP model with those measured in the prototype was one of the main aims of phase C.

7.1.1.3 Phase C

Phase C of the framework has three objectives:

- To ensure that the LP-based prototype meets the pre-set macronutrient requirements (method discussed in sub-study 2);

- To test, in as controlled trial, the level of acceptability and safety of the LP-based prototype (sub-study 3);

- To ensure that the density of the micronutrients meet the specifications in the final RUF; when their requirements are not available, these must be separately determined (sub-study 4)

In the LP-based prototype, the macronutrients must be as close as possible to the requirements pre-determined for the target group. Therefore, the prototype macronutrients were analysed in a laboratory specializing in food analysis.

In our case study, the prototype macronutrients were found to be within the acceptable pre-set range. However, if this had not been the case, the sensitivity analysis tool, described in the same sub-study, could have helped to identify how to improve the LP model settings, if necessary by relaxing some of the constraints and re-running the LP model. In the algorithm on Figure 29, the dotted arrow describes this path. The macronutrients in the second optimized formulation would have been re-tested as an additional check.

The texture parameters, described in sub-study 2, also need to be assessed. In our case study, the texture met the pre-set standards. However, if this had not been the case, the LP sensitivity analysis tool could also have helped here.

Once both the macronutrients and the texture were considered satisfactory, the prototype acceptability and its safety had to be confirmed. They were compared in a crossover-controlled trial in which two groups alternately received the prototype (intervention; SMS-RUTFh) and the current most frequently used product (control; P-RUTF). The strengths and weaknesses of this study design were discussed in sub-study 3. In our case, the level of acceptability and safety were found to be sufficiently high for the optimized formulation.

The RUF product is ready to be clinically trialled only when its micronutrient densities meet the pre-set requirements for the target group. When these are known, a premix can be designed.

However, the micronutrient requirements may not be available. In this case, sub-study 4 suggested a method to determine the specifications of the final formulation for the RUF. Those are based on relevant clinical trials, or their systematic reviews, enrolling study participants, whose characteristics and form of malnutrition are as close as possible to the

target group for the improved RUF spread. In our case study, twenty-three micronutrient specifications were proposed. The limitations of the described method are case-specific, and the sub-study 4 discusses them in depth.

Once mixed with the optimized formulation prototype, micronutrient fortificant powders may change the final taste of the RUF. For this reason, before proceeding with clinical trialling, a sensory analysis should be undertaken. If taste-related issues arise, alternative chemical forms that are commercially available, should be identified in consultation with the premix supplier.

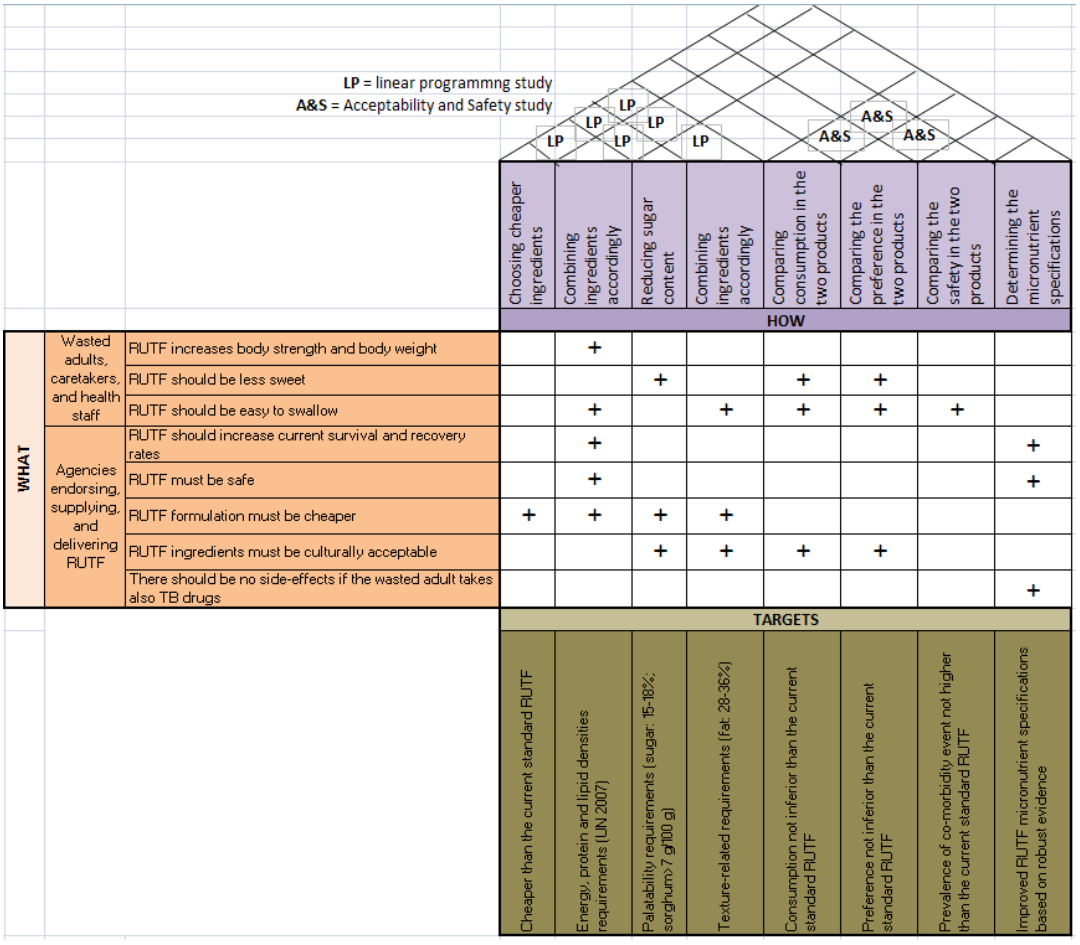
7.1.2 The Quality Functional Deployment model

In the development of the design and validation framework described above, I was guided by existing models and frameworks that are currently in industry. One of the these is the Quality Functional Deployment Model (QFD) approach, which is widely used to improve both food and non-food industrial product design [461]. The following sections describe how the QFD informed the development of the framework described above.

As described in the literature [462,463], the "QFD house" contains, in sequence, three elements called WHATs, TARGETs and HOWs (Figure 30).

In the section called WHAT, the product users inform the designer about *what* to improve in the current standard RUTF (Figure 30). Based on the sub-study 1, wasted adults, caretakers

Figure 30 - Quality Functional Deployment model for the design of an improved ready-to-use therapeutic food to rehabilitate wasted adults living with HIV and/or with TB.



and health staff members expressed the need for RUTF "to increase body strength and weight", for a decreased sweetness and for a texture making swallowing easy. The WHAT section also included other elements. Among the agencies endorsing, supplying and delivering RUTF to HIV/TB wasted adults, there is a demand for an increase in survival and recovery rates. The product should be also safe and cheaper than the current formulation, possibly formulated with locally available ingredients, which, therefore, may better meet the patients' taste and preferences.

For each element, reported in the WHAT section, I identified specific *quantitative objectives*, which are included in the TARGETS section of Figure 30. These included meeting pre-set palatability (sugar 15-18%; sorghum >7 g/100 g) and UN 2007 macronutrient requirements. Nonetheless, in the comparison with the current standard, the product had to comply with a lower cost (USD/kg), a texture based on a fat content of 28-36 per cent, an equivalent or higher consumption or preference rate, and an equivalent or inferior co-morbidity event incidence. In the study group, based on the available literature, I assumed that improved micronutrient specifications would lead to a reduction of side-effects in adults taking TB drugs, and an increase in survival and recovery rates. Therefore, the related TARGET, in the lack of micronutrient requirements, consisted in determining product specifications, set on robust scientific evidence.

In the following step, I identified ways (called HOWs in the QFD approach) to achieve each TARGET (see in Figure 30). For this purpose, during the formulation phase, I proposed to decrease the sugar level, introduce sorghum, and optimize the combination of cheaper, but nutritious ingredients in order to meet pre-set requirements of macronutrients and texture. To confirm the increase, decrease or equivalence of the pre-set TARGETS based on the current standard (P-RUTF), I compared the latter with the novel formulation, which were given to, respectively, a control and an intervention study groups. In the absence of micronutrient requirements for the target group, I developed a method, based on robust scientific evidence, in order to achieve improved RUTF specifications.

In the "QFD roof" (Figure 30), I identified which activities, from the HOW area, could be clustered for convenience. The HOW activities were grouped into the sub-studies 2, 3 and 4. That was done because the linear programming sub-study could simultaneously tackle the choice of the ingredients, their constrained formulation, and the improvement of the ultimate RUTF taste. The sub-study no. 3 (cross-over trial), contained study activities related

to comparisons of consumption, preference and safety in the two products. Only the determination of micronutrient specifications required a separate study activity (sub-study no. 4).

According to a well implemented QFD approach, each element-for-improvement, expressed initially in the WHAT section, must have a correspondent activity (HOW). This can be verified in the central area of the QFD matrix (Figure 30), where each WHAT must have at least one intersection with at least one HOW. The intersection is symbolized by a cross ("+"). Rows, or columns, without a cross would suggest respectively that the final matrix failed to achieve one improvement, or that one study activity was not needed. In my study case, the proposed QFD met all the pre-set improvement goals, and all the activities were consistently object-driven.

For the purposes of this thesis research, the QFD approach, summarised in Figure 2, represented an efficient tool for planning purposes. The QFD matrix suggested an ideal sequence of steps to take in order to design and pre-test novel RUF formulations, allowing efficient grouping of the needed activities, therefore, limiting any waste of resources. However, I considered the illustration tool in Figure 29 more appropriate and user-friendly than QFD (Figure 30), in describing the final design and validation process of RUF products.

7.2 Generalizability of the findings

7.2.1 Criteria to define the generalizability of the findings in public health research

In addition to the case study presented in this thesis, the proposed design and validation framework may contribute to improve the design of other types of RUF products. It is hoped that these may be used to rehabilitate and/or prevent forms of malnutrition, in settings, and in life-stage groups which differ from the ones described here. However, prior to this, the

Table 27 - Definitions of internal and external validity, applicability and transferability.

Term	Definition
Internal validity	The likelihood that study results are valid for the original study population.
External validity	The likelihood that study findings could be generalized to other (unspecified or more general) samples or settings
Applicability	The likelihood that an intervention could be implemented in a new, specific setting
Transferability	The likelihood that the study findings could be replicated in a new, specific setting (i.e. that its effectiveness would remain the same)

Source: definition reported by Dekkers *et al.* [486], and Burchett *et al.* [466]. Some definitions were adapted from [487–489].

generalizability of any innovative method must be proved, before decision makers and donors can endorse it.

In public health, the definition of generalizability, and the criteria to measure it, are a current concern [464–467], because of their complexity. The literature reports at least four terms associated with the concept of generalizability (see in Table 27). Those include internal and external validity, applicability and transferability.

The internal and external validity is the likelihood that study results may be valid respectively only within the original study population, or in any other setting. A study intervention can be considered "applicable" when its results are valid in a limited number of different settings. Moreover, study findings are "transferable" when their effectiveness level does not change, if replicated in another setting.

The method proposed was tested only in on one study group and in one setting. However, encouraged by the results encountered in this thesis, I have applied the proposed method in other world regions and study populations. In most cases, the purpose came from implementing agencies, and their urgent demand for improved formulation solutions. The outputs consisted of the design and the pre-testing of novel RUF spread formulations, designed for other forms of malnutrition, and targeting other age groups and geographical settings. Although not driven by the same research goal, the application of the method proposed in this thesis is this way is helping to define the level of "applicability" or "transferability" of its results to other contexts.

For this reason the following section summarizes the experiences gained from implementing the developed framework in other settings.

7.2.2 Experiences in implementing the developed framework in other settings

In Sri Lanka in 2009, in in collaboration with the local Medical Research Council, and with funds from Irish Aid, a formulation based on soy, rice, milk powder and lentils was designed, and its acceptability and safety pre-trialled among children from a slum in Colombo. The research protocol followed the methods described in sub-study numbers 3 and 4 of this thesis. However, the control products were both Plumpy'nut and BP-100. The collected data showed that the criteria for consumption, safety and preference met the minimum parameters [144]. Furthermore, both the novel formulation and Plumpy'nut® showed a similar

weight gain, significantly superior to the one found when providing BP100. The limitations of the study were no different to those observed in sub-studies 2 and 3 of this thesis. At the current moment, the formulation is to be tested for its effectiveness in Bangladesh by an international NGO. More information about the design and the pre-testing study are available in a published paper, available in annexes.

In 2010, in Vietnam, in collaboration with the national Nutrition Institute, a formulation based on soy, rice, mung beans and milk powder was designed based on the findings from sub-study number 2. The formulation is currently being tested for its acceptability, safety and effectiveness by other research institutions.

Five formulations were designed for the sub-Saharan African region, but for forms of malnutrition different from the one of my case study.

- One RUCF spread contained sorghum and maize, while a second also included milk powder and sorghum. In 2012, the findings comparing the latter with a fortified porridge were reported in a peer-reviewed journal [234] (the paper is available in annexes). No difference was noticed in terms of preventing stunting between the intervention and the control groups. A side-study based on the same formulations and on the deuterium-dose-to-the-mother dilution technique showed no reduction in breast-milk intake associated with the RUCF [106].

- Whey protein concentrate (WPC) is cheaper than milk powder. Two forms of WPC (34, and 80% protein content) were tested for replacing milk powder in three RUTF formulations, in Zambia. One of these (whey protein at 80%) was based on maize, soy and sorghum, whereas the other two contained peanut butter (whey protein at 34 and 80% respectively). Their prototypes are currently being tested.

- One SMS-RUTF was trialled in wasted Zambian children. It contained the food ingredients of the product described in this thesis, and met the pre-set macronutrient specifications of UN 2007 for RUTF. The acceptability of the product was reported in a peer-reviewed paper [146]. The findings from its effectiveness trial are still to be released.

7.2.3 Conclusions about the generalizability of the framework

In spite of the successful application of the proposed method in at least six study populations and settings, the generalizability of the framework cannot be taken for granted. This is because these studies were not purposively designed to measure its level of replication. Furthermore, there is limited consensus about the criteria to use to determine the level of study generalizability [464–467].

However, it can be argued that the applicability of the proposed method seems to be promising, at least in the regions and for the groups where the proposed framework to improve the current RUF spreads was applied.

7.3 Implications of this study

Potentially, the findings of this thesis have direct implications for institutions in both the public and private sectors.

As described in section 1.3.3, in the public sector, policy makers, donors, and humanitarian agencies have voiced the urgent need for a framework to design and validate improved and cheaper RUF formulations. Moreover, their recommendations for further research coincided with the identified knowledge gaps tackled in this thesis. Since the applicability of our findings was documented, representatives from the public sector may consider endorsing versions of the proposed design and validation framework.

In the private sector, there may be demand for the proposed framework among global and local food manufacturers at different levels and scales. In 2012, the manufacturers qualified to distribute RUTF, based on the UNICEF Supply Division requirements, were nineteen [94] and "expected to increase in the coming years, especially in countries where RUTF is used" [94]. The World Bank expects these firms to be fuelled by economic sources including "government finances, private sector corporations, and international financial aid" [40]. However, the proposed framework will become a successful practice only if "the development, evaluation, and promotion of these foods are at the interface of private and public interests" [269].

7.4 Acknowledgement of limitations

The method described here showed some limitations.

In the sub-study 1, which looked at the HIV positive patients' adherence within a RUF-based nutrition rehabilitation programme, clinical information about the patients could not be collected. This may have helped in understanding the impact of RUF-based approach in presence of household/community sharing, food mixing, lack of counselling, and clinical difficulties in swallowing.

The sub-study 2 described the application of a mathematical model approach to formulate an improved RUF product. Although the proposed approach achieved its goal with one constraint adjustment, the economic aspects of the choice of the ingredients, the impact of using alternative food composition databases and the advantages of more complex mathematical models may have improved the proposed approach. In particular, future models should include maximum level constraints of anti-nutritional factors, or minimum levels of dairy product derivates.

In the sub-study 3, which described a method for trialling the acceptability and safety of a novel RUF formulation, the conclusions may have been limited by the relatively short duration of the study, by only one-meal observation per day, and by the fact that the study participants may not be representative of the future RUTF beneficiary group, because they were not malnourished.
Furthermore, in the proposed method framework, the RUF spread does not contain the micronutrient premix, because the premix is designed and procured on the basis of a formulation already proved acceptable. This means that the proposed framework fails to test whether the presence of the premix negatively influences the preference and the consumption of the improved product.

The sub-study 4 described the development of a method for determining the micronutrient specifications for a RUF-based supplement. However, the evidence used to determine the specifications were based on studies which were heterogeneous. Therefore, the compiling of the results has been challenging. In view of this, the validity of the method must be confirmed.

The overall method described in this thesis is consistent with the use of the QFD model, which also showed some limitations. For instance, QFD does not address the fact that food "raw materials show a natural predisposition for variation" which does not tally with the

somewhat inflexible character of QFD charts regarding changes [462,468]. This same problem was confirmed, in section 4.9, by the limitations of the food composition databases used to optimize the LP model. Furthermore, QFD does not capture the *interactions* among the attributes listed by the consumers, limiting the potentiality of the method.

7.5 Recommendations for further research

The proposed method raises many questions for several areas of further research. The following sections list them, describing their importance.

7.5.1 Quality standards

Research question – *how should the current safety standards be improved for RUF spreads, in view of the higher morbidity and mortality risks of the consumers?*

As described in section 1.4, standards for RUF to guide the manufacturers' activities are currently missing. So far, agencies like MSF and UNICEF have relied on the current practice codes designed by Codex Alimentarius for children's food products formulated, processed and packaged for the western market. However, the settings and the consumers of RUF spreads may be different and often inapplicable from the point of view of the current standards. Therefore, a tailored approach may be needed. Among the most urgent specifications required are protocols to determine the shelf life of these products, and of their micronutrients, taking into account the extreme conditions (i.e. temperature, transport, etc.) of the humanitarian food supply chain.

Research question – *how can field-based, quick and reliable quality tests (microbiological and chemical) be developed to ensure the efficacy and the safety of RUF products?*

In wasted people, the adequate concentration of micronutrients is crucial to achieve nutritional rehabilitation and increase survival [28]. Microbiological safety is a great concern in the target populations, because RUF is consumed without cooking. Bacterial contamination, harmless in healthy people can be fatal in wasted human beings.

However, food quality laboratories in developing countries have a limited capacity to perform both these kinds of analysis. This was confirmed by a recent study

looking at the development of one RUF spread in Africa [146]. Quick, cheap, and portable tests should therefore be urgently designed and produced to allow operators in the field to check on the RUF safety before its delivery. They should come with acceptable ranges for each key nutrient of the RUF product.

7.5.2 Optimization of micronutrient absorption, digestibility, processing, and packaging

Research question – *in wasted people, what is the true level of absorption of micronutrients from RUF premixes?*

In undernutrition research, little is known about the real level of micronutrient absorption. This might be because the research methods for this kind of study are costly and complex to implement [469]. This last issue may present an additional challenge in low-resource settings. In the available literature, some authors [28,174] suggest lists of chemical forms for most micronutrients to be included in foods used in feeding programmes. However, their absorption ratio remains undocumented. This matters for each micronutrient. Studies identifying the optimal chemical form for both type I and II micronutrients for RUF formulation are urgently needed in order to optimize their absorption.

Research question – *can the digestibility of RUF products be monitored and, if needed, increased?*

Little is known about the current level of digestibility in undernourished patients, when fed with RUF products. UNICEF Supply Division and MSF consider food aid plant-based items digestible when their level of pre-gelatinized carbohydrate is at least 80 per cent. In low-income countries, the choice of technologies to gelatinize the starch, in flours with cereals and legumes, are limited and often expensive.

Our study suggested that extrusion was ideal in the considered study case setting. However, nausea and vomiting were more frequent in association with RUTF containing extruded soy, maize, sorghum rather than milk powder and roasted peanut in not wasted adults.

In general, little is known about the implications of processing technologies on the digestibility in undernourished people. Only one study was found looking at digestibility improvement using different techniques to process food aid items. This study [285] compared the starch digestibility of a blended corn-soy flour mix, prepared with and without extrusion cooking. The study was conducted in eight healthy volunteers, using ^{13}C enrichment of breath samples for 8 hours, measuring breath H_2 concentration during 12 hours to assess bacterial fermentation in the colon, and asking the volunteers to report hunger on a visual scale during eight hours at intervals of four hours. The conclusions suggested that extrusion did not seem to substantially improve blended foods digestibility and may promote carbohydrate fermentation in the colon and increase satiety.

However, other techniques, such as infra-red or micronization, that exist in some low-income countries and may be used in combination with extrusion, may provide cost-effective solutions to improve digestibility of RUF. Endorsed protocols are urgently needed to assess digestibility of RUF in the undernourished.

Research question – *which context-specific options can be developed for the processing and packaging of RUF so as to extend shelf life?*

Section 1.3 reported how RUF production is getting closer to the areas where it is used. This approach has implications for the final RUF costs. Beside the ingredients and transport, the processing and the packaging are the most expensive steps, and they influence the product shelf life. With nitrogen-flush packaging, for instance, the spread can be safely consumed after two years from the production [470]. However, the machinery needed "is the most expensive component of a RUTF production line" and, RUF spreads packed with non-airtight sachets will need to be consumed within a few months, limiting their utility [470]. This is an additional challenge "when storage and transportation are unpredictable" [470]. There is, therefore, a demand for the development of appropriate technical solutions.

7.5.3 Cost-effectiveness analysis

Research question – *what are the criteria to assess the cost-effectiveness of improved RUF formulations?*

The findings from cost-effectiveness analyses may better guide health and nutrition policies and practices. This is because "the ratio of net health-care costs to net health benefits provides an index by which priorities may be set" [471]. Cost-effectiveness was only found described in a few studies, which were limited to one type of RUTF [472–474] and focused on the programme rather than the product. It can be speculated that with a proliferation of formulations, the economic perspective will assume increasing importance. However, at present no internationally endorsed cost-effectiveness method is available to support decisions on which RUF formulations to use in feeding programmes.

7.5.4 Use of probiotics, prebiotics or synbiotics in RUF

Research question – *is there any benefit in adding probiotics, prebiotics or synbiotics to RUF spreads destined for wasted HIV positive people?*

Conflicting evidence surrounds the use of probiotics, prebiotics and synbiotics. Recently, Cunnigham *et al.* [475] report increasing evidence that "probiotics bacteria may stabilize CD4 cell numbers in HIV-1 infected children and are likely to have protective effects against inflammation and chronic immune activation of the gastrointestinal immune system". In most studies, probiotics and their derivates were mostly provided in liquid-based food carriers. When offered to the consumer in a RUF spread, the results were less positive. Kerac *et al.* [152,476] report that in an African, HIV-prevalent setting, a specific type of synbiotics "did not improve severe acute malnutrition outcomes". However, the same study highlights that a "subgroup analysis showed possible trends towards reduced outpatient mortality in the symbiotic group". The authors suggest that this "might be caused by bias, confounding, or chance, but is biologically plausible, has potential for public health impact, and should be explored in future studies".

The commercial strains and genetic types of pro-, pre- and synbiotics available on the market are many. It can be speculated that some strains may be more vital and effective than others in the RUF food matrix. Their vitality may also vary during the shelf life of the RUF, and the adequate dose needed is not known. Further studies are required to investigate their efficacy and effectiveness.

7.5.5 Legal definition and protection

Research question – *how to define RUF products from the legal point of view?*

Categories of foods are described by international organizations to ease transnational trade operations. Today, RUF products are global products with an increasing regional consumption among vulnerable people in low-resource settings. However, RUF items do not yet benefit from a formal legal recognition framework, and no legal definition of RUF is currently available. Section 1.3.1.1 of this thesis identified some common elements between the definition of RUF and functional foods. However, further research in this area is urgently needed, and should include the implications for future policy and practice.

Research question – *what policies and practices are necessary to legally protect RUF formulations in view of its urgent humanitarian use?*

According to the available evidence, the patenting of RUF products seems to delay their availability on the market, thereby limiting the rehabilitation of people in need. The impact of this approach was not documented sufficiently and possible alternatives need to be further explored. However, new legal forms aiming to protect innovations, while guaranteeing their open-access, are currently being developed. Pre-agreed Licensing, like the one between Valid Nutrition and Nutriset, is a promising example, but more comprehensive legal solutions to ensure prompt and wide geographical disposal of RUF are crucial.

Recently, the number of scientific publications filling current knowledge gaps about the use of RUF in treating and preventing undernutrition has increased. Based on the literature[477,478] published before this thesis submission, the list of research questions for the development of improved RUF products should include:

- How to determine the micronutrients specifications taking into account the phytate contents of the RUF ingredients?
- How to measure the risk of aflatoxin-based morbidities associated to RUF products?
- What is the minimum amount of expensive ingredients (e.g. milk powder) in RUF

products to achieve still cost-effectiveness?

- What are the risks and the strengths of RUF-based interventions in contexts presenting *nutrition in transition*?

7.6 Summary of the main conclusions

This thesis designed and pre-tested an innovative method to improve cost-effective RUF spreads for the prevention or treatment of undernutrition, prior to subsequent clinical trialling.

The proposed method was:

a. *tested* on a case-study, which consisted of the design of a low-cost, acceptable and safe RUTF, specific for wasted adults, living with HIV with (or without) active TB;

b. *unpacked* into four sequential sub-studies:

- ***Sub-study 1*** concluded that the level of reported compliance with the prescribed dose of the current standard RUTF was low. Based on the collected evidence, an improved approach to treating malnourished HIV-positive adults in limited resource contexts is needed and must consider strategies to support patients without a caregiver, development of therapeutic foods more suited to adult taste, and specific dietetic training for health staff.

- The conclusions of the ***sub-study 2*** were that a mathematical approach called linear programming can contribute to the design of RUF (therapeutic, supplementary, or complementary), targeting different forms of malnutrition, while using commodities that are cheaper, regionally available, and meeting local cultural preferences.

- ***Sub-study 3*** reached the conclusion that the improved RUTF prototype from sub-study 2 appears to be acceptable and can be safely clinically trialled, if close monitoring of vomiting and nausea is included.

- ***Sub-study 4*** concluded that the developed method used to determine the specifications of vitamins and minerals to be included in a RUF may be limited by the heterogeneity of the available RCT studies. However, some evidence was found that multiple micronutrients, provided in a high-dose, were associated with positive health outcomes and survival. In view of this, although the doses used in the selected studies informed the novel specifications, the validity of the proposed method needs to be confirmed.

Based on the four sub-study outcomes, I developed a framework that summarizes the entire process to develop, pre-test and clinically trial novel RUF products.

Opportunities for future research should be taken. These should focus on the RUF quality standards, on the optimization of the absorption and digestibility of the micronutrients, on the processing, the packaging, the cost-effectiveness analysis, the legal definition and protection of RUF formulations.

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9 Appendices

9.1 Research articles

9.1.1 Directly related to this thesis

With first authorship of the PhD candidate:

1. Dibari F, Bahwere P, Huerga H, *et al.* Development of a cross-over randomized trial method to determine the acceptability and safety of novel ready-to-use therapeutic foods. *Nutrition* 2013; **29**: 107–12.

2. Dibari F, Diop H, Collins S, Seal A. Low-Cost , Ready-to-Use Therapeutic Foods Can Be Designed Using Locally Available Commodities with the Aid of Linear Programming. *The Journal of nutrition* 2012; **142**: 955–66.

3. Dibari F, Le Gall I, Guerrero S, Mwaniki D, Seal A. A qualitative investigation of adherence to nutritional therapy in malnourished adult AIDS patients in Kenya. *Public Health Nutr* 2012; **15**: 316–23.

4. Dibari F. Acceptability trial of a novel RUTF based on soy, lentils and rice. *Field Exchange* 2010; **39**: 12–3.

With co-authorship of the PhD candidate:

1 Irena AH, Bahwere P, Owino VO, Victor O. Owino, ElHadji I. Diop, Max O. Bachmann, Clara Mbwili-Muleya, Filippo Dibari, Kate Sadler and Steve Collins. Comparison of the effectiveness of a milk-free soy-maize-sorghum-based ready-to-use therapeutic food to standard ready-to-use therapeutic food with 25% milk in nutrition management of severely acutely malnourished Zambian children: an equivalence non-blinded cluster randomised controlled trial. *Maternal & child nutrition* 2013.

2 Owino VO, Irena AH, Dibari F, Collins S. Development and acceptability of a novel milk-free soybean-maize-sorghum ready-to-use therapeutic food (SMS-RUTF) based on industrial extrusion cooking process. *Maternal and Child Nutrition* 2012; **in press**.

3 Bisimwa G, Owino VO, Bahwere P, *et al.* Randomized controlled trial of the effectiveness of a soybean-maize-sorghum–based ready-to-use complementary food paste on infant growth in South Kivu, Democratic Republic of Congo. *The American Journal of Clinical Nutrition* 2012; **95**: 1157–64.

9.1.2 Presentations to meetings and conferences

- **Action Against Hunger** - Hunger Talks. October 2012. London
  → 'Linear Programming: A Nutritional Perspective – watch on http://goo.gl/w79Gg

- **Medicus Mundi** - "An Ideal Match?! Connecting NGOs and Academia in Research for Global Health". September 2011. Amsterdam.
  → A cheaper ready-to-use therapeutic food (RUTF) specific for wasted adults living with HIV/TB in low-income countries: a randomised clinical trial testing its effectiveness in an MSF/Holland programme (Zimbabwe).

- **Gain Regional Forum** – Johannesburg 2010
  → Is it possible to rehabilitate adult HIV/TB wasting in high prevalence rural areas? An on-going Kenyan experience – watch on http://goo.gl/LoZoM.

- **Rank Prize** - Mini-symposium on Nutrition and HIV. Winderemere, UK 2009
  → *Operational aspects of therapeutic nutritional rehabilitation for HIV/TB patients: the use of ready to use therapeutic foods*

- ***39th Union World Conference on Lung Health*** *– Paris October 2008*
  → *Operational aspects of therapeutic nutritional rehabilitation for HIV/TB patients: the use of ready to use therapeutic foods*

- **5th TICH Annual Scientific Conference**. Kisumu, Kenya May 2008
  → Are UN nutrient requirements for adults living with HIV appropriate when applied to nutritional therapy for the severely malnourished?

- **FAO/HQ** – Rome, September 2007
  → HIV & severe acute malnutrition: improvements in the use of Ready to Use Foods in limited-resources contexts

- **Concern International, Irish Aid and WFP** - Inter-agency Consultative Group Workshop - Food Assistance Programming in the Context of HIV, Food Assistance in the Context of HIV Handbook Review. Dublin December 2006.
  → Are UN nutrient requirements for adults living with HIV appropriate when applied to nutritional therapy for the severely malnourished?

9.2 Study-related material

9.2.1 Ethical approval of the Kenyan studies

KENYA MEDICAL RESEARCH INSTITUTE

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KEMRI/RES/7/3/1 **JULY 29, 2008**

FROM: **SECRETARY, KEMRI/National Ethical Review Committee**

THRO': **Dr. Yeri Kombe,**
CENTRE DIRECTOR, CPHR,
NAIROBI

TO: **Fillipo Dibari & David Mwaniki (Principal Investigators)**

RE: **SSC No. 1414 (Rev):** A randomized controlled no-inferiority trial of a low cost nutrient dense food for malnourished HIV positive Kenyan adults being treated with standard ART

Dear Sirs,

This is to inform you that during the 156th meeting of KEMRI/National Ethical Review Committee held on 29th JULY 2008, the above referenced study was reviewed.

The Committee notes this is a randomized controlled trial on moderately and severely malnourished adults living with HIV and on ART in the Homa Bay area. The aims are threefold:

1. To assess the efficacy of a "Ready to use Therapeutic Food (RUTF: soy, sorghum and maize) versus Plumpynut (peanut butter, lactoserum, maltodextrin and skimmed milk powder) in malnourished adults
2. To measure the livelihoods of the patients household
3. To determine the acceptability and affordability of the novel formulation RUTF

Due consideration has been given to ethical issues except for the absence of the contact of the KEMRI/NERC in the Informed Consent Document that allows the research participant to contact the committee incase they have a question about their rights of participation. Kindly address the above issue and remit a revised proposal to the secretariat for further action.

Respectfully,

RCKithinji

R. C. Kithinji,
For: Secretary,
KEMRI/NATIONAL ETHICAL REVIEW COMMITTEE

9.2.2 Compliance study

[071114]

QUESTIONNAIRE – Patient **I.D. CODE: _____**

Date: __/11/2007 Starting time: ___:___ Finishing time: ___:___
Name translator: _____Place: _____

Key informant information [patient]:

Consent given [yes/no]	FUCHIA No.	Age	Sex	Married [Yes/No]	Widow [yes/no]	Children [number]	Hiv/TB	Under Plumpynut [yes/ex]	With a buddy or a carer [yes/no]

1. What did you receive for the treatment of your *thinness*? [Question 1.b]
   - ☐ Nothing → stop
   - ☐ Afya → stop
   - ☐ Plumpynut® → [Question 1.b]
   - ☐ Foundation+ → stop

1.b According to you, is Plumpynut® a food ☐ or a drug ☐? → [Question 2]

2. How much Plumpynut® did you receive for the treatment? _____ sachets/day

3. What did the medical staff tell you about the Plumpynut®?
   - _____
   - _____
   - _____
   - _____
   - _____

4. Could you eat all the sachets per day that the medical staff prescribed?
   - ☐ Yes → [Question 5]
   - ☐ No → [Question 7]

5. What are the DISADVANTAGES provided by the Plumpynut®? [→ Question 6]
   - _____
   - _____
   - _____
   - _____
   - _____

6. What are the ADVANTAGES provided by the Plumpynut®? [→ Question 8]

- _____
- _____
- _____
- _____
- _____

7. Why you could not apply the indications suggested by the medical staff? [→ Question 5]
   - _____
   - _____
   - _____
   - _____
   - _____

8. Did you manage to eat all the amount of Plumpynut® prescribed per day?
   - ☐ Yes → [Question 9]
   - ☐ No → [Question 12]

9. Did you mix the Plumpynut® with other food?
   - ☐ Yes → [Question 10]
   - ☐ No → [Question 13]

10. Which food did you mix the Plumpynut® with? [→ Question 11]
    - _____
    - _____
    - _____

11. What was roughly the proportion of mixing? [→ Question 13]
    - _____
    - _____
    - _____

12. Why did you not manage to eat the prescribed amount of Plumpynut®? [→ Question 9]
    - _____
    - _____
    - _____

13. What do you think about the packaging of Plumpynut®? [→ Question 14]
    - _____
    - _____
    - _____
    - _____
    - _____

14. How would you IMPROVE the Plumpynut® in terms of: [→ Question 15]
    - Taste?----------
    - Consistence?----------
    - Smell?----------

- Packaging? ----------

15. Did you make other people taste the product?
    - ☐ Yes → [Question 16]
    - ☐ No → [Question 17]
16. Who were they? [→ Question 18]
    - ☐ Children → comments? ----------
    - ☐ Adults → comments? ----------
17. Why you did not want to make other people taste the Plumpynut®? [→ Question 18]
    - _____
    - _____
    - _____
18. Please, can you share a negative STORY related to Plumpynut®? [→ Question 19]
    - _____
    - _____
    - _____
19. Please, can you share a positive STORY related to Plumpynut®? [→ Question 20]
    - _____
    - _____
    - _____
20. What did you normally eat in the same day beside the Plumpynut®? → stop
    - _____
    - _____
    - _____

[071116]

FOCUS GROUPS GUIDE – Medical staff

Date: __/11/2007 Starting time: ___:___ Finishing: ___:___

Facilitator: _____ Transcriptor: _____

Place: _____

Participants:

Consent [Yes/no]	Participant name	Age	Sex

GUIDE

- General introduction / presentation of the participants
- Purpose of the FG

1. What do people in Homa Bay normally eat? 2. What do people eat when they have AIDS/Ukimwi? 3. According to people's opinion, does HIV cause people to become thin? [Ukimwi] 4. What do you think people should eat when they have AIDS/Ukimwi? 5. What advice do people receive on eating when they have AIDS/Ukimwi?	
6. Do you know what this is [wave a sachet of Plumpynut®]? What is it for?	
7. Is it useful? 8. Is it useful for people being treated for AIDS/Ukimwi? 9. Is it a drug or a food? [Voting with the dynamic of the *single-bean* in two cups]	
10. How many people in the group have received Plumpynut®? 11. Have you eaten Plumpynut®? 12. How much Plumpynut® do people eat per day? [no. sachet] 13. For how many days/weeks/months do people eat Plumpynut®? 14. When people eat Plumpynut®, do they mix it with other foods? 15. If so, why do they mix Plumpynut® with other foods?	
16. Do people use Plumpynut® differently if they are inpatients or outpatients?	
17. Have you heard of any particular story related to the consumption of Plumpynut®? [positive/negative aspects]	
18. Which sort of Plumpynut® would people with AIDS/Ukimwi probably prefer? [taste, colour, smell, consistency, packaging]	

[071114]

FOCUS GROUPS GUIDE – Patients and carers

Date: __/11/2007 Starting time: ___:___ Finishing: ___:___
Translator: _____ Transcriptor: _____
Place: _____
Participants:

Consent [Yes/no]	Participant name	Age	Sex	Married [Yes/No]	Widow [yes/no]	Children [number]	Hiv/TB	Plumpynut [yes/ex]	FUCHIA No.

GUIDE

- General introduction / presentation of the participants
- Purpose of the FG

1. What do people in Homa Bay normally eat? 2. What do people eat when they have AIDS/Ukimwi? 3. According to people's opinion, does HIV cause people to become thin? [Ukimwi] 4. What do you think people should eat when they have AIDS/Ukimwi? 5. What advice do people receive on eating when they have AIDS/Ukimwi?	
6. Do you know what this is [wave a sachet of Plumpynut®]? What is it for?	
7. Is it useful? 8. Is it useful for people being treated for AIDS/Ukimwi? 9. Is it a drug or a food? [Voting with the dynamic of the *single-bean* in two cups]	
10. How many people in the group have received Plumpynut®? 11. Have you eaten Plumpynut®? 12. How much Plumpynut® do people eat per day? [no. sachet] 13. For how many days/weeks/months do people eat Plumpynut®? 14. When people eat Plumpynut®, do they mix it with other foods? 15. If so, why do they mix Plumpynut® with other foods?	
16. Do people use Plumpynut® differently if they are inpatients or outpatients?	
17. Have you heard of any particular story related to the consumption of Plumpynut®? [positive/negative aspects]	
18. Which sort of Plumpynut® would people with AIDS/Ukimwi probably prefer? [taste, colour, smell, consistency, packaging]	

9.2.3 Acceptability and safety study

9.2.3.1 Informed Consent

Check list of contents for the study subject consent

Survey Information Sheet for Requesting Participants Consent - IMPORTANT for the ADMINISTRATOR or the information sheet (to read BEFORE starting):

Explain the following topics ONLY if:

- the patient is ABLE to understand them. I.e.: same language of the speaker (DhoLuo, or English, etc.), healthy mental status, not under drugs, etc.
- TIME is available to explore all the different aspects, including answering to possible questions

TOPICS to cover for informed consent:

(please tick on the little box beside)

The University of London and Valid International are working together with MoH, MSF, KEMRI and other implementing partners to promote the nutritional status of the adult population in the Homabay area who are malnourished and who are also living with HIV. The aim of the survey is to test a new nutritional therapy specific for people are malnourished and who might be having the virus of HIV and therefore in need of ART.	
The new nutritional product will be tested in this first phase of the study on patients who are HIV+, under ART but who are not malnourished or in complex clinical conditions	
If you decide not to participate to the study you will still receive the routine health care	
Two different therapeutic nutritional products are now available and being tested. The old one is currently used by MSF when adults or children are malnourished disregarding their HIV status. A new one has been designed specifically for people living with HIV and may help to decrease the possibility of infections and produce quicker weight gain.	
You will be not told which nutritional therapeutic product you are given to make the results of the study more objective. But, if you wish, you can request to know which one you have received at the end of the study.	
The new product is very similar to the old one, but is cheaper and has different amounts of vitamins and minerals. It is expected to be at least as good as the old kind of product or even better.	
The risk of the new product being at all harmful has been minimized as much as possible by carrying out various analysis on the product	
If the new product is found to be more efficient than the old one in helping people living recover and gain weight many people in the whole world will benefit enormously from it.	
If the new product will perform just as well it will be still good because the new one is cheaper than the old one so more product can be produced and more people can benefit.	
If you decide to take part in the survey you may choose to stop participating at any time you wish and nothing bad will happen. You will continue to receive any food aid and/or health care you are already getting in the normal way.	
If during your treatment you delay in coming to the clinic, somebody from our team will try to call your phone number (if any) and to try to understand the reason for your defaulting.	

If you do not want this to happen now or later, you will be still entitled to participate to get full medical assistance	
During the study you may be invited to be interviewed about problems you faced along the consumption of the food. Your opinion will be very important to allow us to improve the product and the delivery service for other people. The opinions you will share with us will be not associated to your identification.	
If you do not want to share your opinions with us, you will be still entitled to participate to the study.	
Please feel free to ask any questions you may have at any time during the study.	
Which criteria for admission? If not respected you will be not admitted – sorry!	
• BMI 18.5 – 20 •	
• Residents or living close to Homa Bay town	
What should I do to participate to the study?	
Every day you MUST come with you the MSF or MoH patient card (**blue** or **yellow**)	
You will come/arrive to the study site (Homa Bay downtown): • between **11:30am** and **13:00pm** and you will remain there only for two or three hours maximum	
• every day (from Monday to Fridaty):	
o from the 30th of June to the 11th of July (2 weeks) and	
o from the 21st of July to the 1st of August (other 2 weeks)	
VERY IMPORTANT: If you will miss more than 2 days: • you will be asked not to come back to the study	
• you will be not admitted anymore	
What will I get during the study?	
you will get free lunch based on Plumpynut or the new product	
you will get clean drinkable water	
you will get a reimbursement of 100 KSh for the transport every day	
you will get a certificate of participation to the study	

VALID

Homa bay: __/__/2008

CONSENT FORM

Title of project:

A randomized controlled non-inferiority trial of a low-cost, nutrient-dense food, for malnourished HIV positive Kenyan adults being treated with standard ART -

Acceptability Trial phase

(Please put your initials in the box)

1. I confirm that I have read and understood the information details of the study provided in information sheet dated for the above study and have had the opportunity to ask questions. *An gi adier ni asomo kendo awinjo andikegi duto maluore gi risachni kendo aydo thuolo mar penjo mondo olerna kwende ma ok awinjo* ☐

2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study *An gi adiera ni ne omiya thuolo moromo mondo ayangi awuon ka adwaro donjo e risachni kata ooyo.* ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. *Angeyo ni donjo e risachni en yiro mara kendo anyalo wuokie samoro a mora mahero ma onge gima aluoro ka luwore gi ngimana mapile* ☐

4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research project team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. *Angeyo ni bugena mag osubtal inyalo ngiyo gi jotich mochungne risachni* ☐

5. I am happy to receive the tracing team in case I do not come to the fixed appointment. *An gi adier ni asomo kendo awinjo andikegi duto maluore gi risachni kendo. Mora mahero ma onge gima aluoro ka luwore gi ngimana mapile* ☐

6. I agree to take part in the above study. *Ayie mondo abed achiel kuom joma odonjo e risachni* ☐

1 form for Patient;
1 to be kept as part of the study documentation,

(Continued on next page)

1 form for Patient;
1 to be kept as part of the study documentation,

Homa bay: __/__/2008

Name of patient (*Nyingi*)	Date (*Tarik)*	Signature (*Seyi mari)*
Name of Person taking consent (if different from researcher) *(Nying ngama ndiko jatuo)*	Date (*Tarik)*	Signature (*Seyi mar jandiko)*
Researcher (to be contacted if there are any problems) *(Nying ngama ochungne risach ma onego wuogo ka nitie wach moro)*	Date *(Tarik)*	Signature (*Seyi mar ngama ochung ne risachni)*

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the **investigator** (Filippo Dibari, Tel. 0728 163455). If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with anyone of the MoH/MSF clinicians **who are fully aware of the study** (tel. 05922401), the **MSF field coordinator** (Tel. 05922401).

Ka ini wach moro amora to inyalo wuoyo gi ngama ochungne risach ni miluongo ni Filippo. To ka wach moro ochuanyi inyalo wuoyo gi to Migawo mag thieth e Homa Bay District kata gi ngama ochungne MSF

9.2.3.2 Data collection forms

A: SOCIO-DEMOGRAPHIC DATA

Survey Id. No. __/__/ Date of interview __/__/2008
First name…….. Age (years) __/__/
Village/Town of residence……
Sex **(1=**Male) (**2**=Female)
Marital status (**1**=Single) (**2=**married) (**3**=separated/divorced) (**4=** widowed.)
Number of children/siblings __/__/
Education Attained/Mother/Father**:**
(1=No formal education)
(**2**=Adult education)
(**3**=Primary school only)
(**4**=primary school + training)
(**5**=A few years in secondary school)
(**6**=Form four only)
(**7**=Form four + training)

(**8**=Form six only)
(9=form six+ training)
(**10**=College/university)

Economic activity/Mother/Father
(**1**=Farming only)
(**2**=trading/artisan)
(3=pastoralist only)
(**4**=farming pastoralist)
(**5**=trading/artisan+farming)
(**6**=Formal employment)
(**7**=informal employment)
(**8**=Disabled or too old.)

Tribe (**1**=Luo) (**2**=kisii) (**3**=kamba) (**4**=Kalenjin) (**5**- Others (Specify:_____)

Religion(**1**= Catholic) **(2**=protestant) (**3**=muslim) **(4**-traditional) (**5**-none)

Phone number(s) for contact (if any) __/__/__/__/__/__/__/__/__/__/

This phone number belongs to (please tick):
(**1**=The client) (**2**=Member of the family of the client) (**3**=Neighbour or other)

B. Socio-economic indicators: living conditions

1 Of which material are the walls of the main house made of? .....
(**1**=mud and wooden pole) (**2**=unburnt mud brick) (**3**=burnt bricks) (**4**= cement or stone blocks) (**5**=iron sheets) (**6**=timber)

2. Which roofing material is your house made of?
(**1**=iron sheets) (**2**=papyrus/grass thatch) (**3**=tiles) (**4**=other (specify:_____)

3. What is your main source of cooking fuel?
(**1**=firewood) (**2**=charcoal) (**3**=paraffin) (**4**=gas) (**5**=electricity)

4. What is your main source of lighting?
(**1**=open fire) (**2**=kerosene burner) (**3**=kerosene lamp) (**4**=electricity) (**5**=gas lamp)
(**6**=others (specify:_____)

5a.Which of the following items do you posses?
(**1**=radio) (**2=**bicycle) (**3**=motor cycle) (**4**=tv) (**5**=car)

b. Do you have any of these animals? (Specify the number)
Goats..... (1=yes) (2=NO)
Sheep..... (1=yes) (2=NO)
Cows..... (1=yes) (2=NO)
Poultry.....(1=yes) (2=NO)
Others (specify)..... (1=yes) (2=NO)

6. Where do your children (brothers/sisters) go to school?
Child 1: __/
Child 2: __/

Child 3: __/
Child 4: __/
Child 5: __/

(1=Public day secondary/primary) (2=private day secondary/primary) (3=Boarding secondary/primary school) (4=Not school going age) (5=read at home)

b) DIETARY DIVERSITY QUESTIONNAIRE

Date: __/__/__/
Survey Id.No.: __/__/ Name:_____

Fluent in Swahili/English (yes=1**) (**No=2**)**

Please describe the foods (meals and snacks) that you ate yesterday from the moment you woke up until when you went to bed, whether at home or outside the home. Start with the first food eaten in the morning. **Diher nyisa chiemo mane miichamo nyoro chakre saa mane ichiewo nyaka saa mane idhi nindo, e odi kata oko mar odi.Chakna gi chiemo mi chamo gokinyi.**

Question number	Food group	Examples	Coding categories
1	CEREALS **Kothe**	Any foods made from millet, sorghum, maize, rice, wheat *(ugali, bread, biscuits, cakes porridge or pastes or other locally available grains.* **Chiemo mora mora molos gi bel, kal, bando,ochele, ngano, kata nyuka mimatho molos gi gigi**.	1 **(YES=1)** **(NO=2)**
2	VITAMIN A RICH VEGETABLES AND TUBERS	pumpkin, carrots or sweet potatoes that are orange inside, sweet pepper and other vitamin A rich vegetables. **Budho, carrot, rabuon ratong gi mamoko**.	2 **(YES=1)** **(NO=2)**
3	WHITE TUBERS AND ROOTS	Irish potatoes, white yams,white sweet potatoes cassava, or foods made from roots. **Gwacho/waru, nduma, rabuon marachar, marieba gi mamoko**	3 **(YES=1)** **(NO=2)**
4	DARK GREEN LEAFY VEGETABLES	dark green/leafy vegetables e.g. amaranthus, black night shade, spider plant, cowpeas leaves, pumpkin leaves, kales, spinach, cassava leaves + other wild ones. **Mchicha/ododo, dek, boo, susa, sukuma,spinach, it marieba, mrende gi mamoko**	4 **(YES=1)** **(NO=2)**
5	OTHER VEGETABLES	other vegetables (e.g. tomato, onion, eggplant) , including wild vegetables **nyanya, kitunguu, gi mamoko**	5 **(YES=1)** **(NO=2)**
6	VITAMIN A RICH FRUITS	ripe mangoes, paw paws, water melon +*other locally available vitamin A-rich fruits* **maembe, poo poo, water melon gi mamoko**	6 **(YES=1)** **(NO=2)**

Question number	Food group	Examples	Coding categories
7	OTHER FRUITS	Oranges, passion, pineapples, Ovacado, bananas, including wild fruits. **Machungwa, ovacado, matunda, rabolo gi mamoko.**	7 **(YES=1)** **(NO=2)**
8	ORGAN MEAT (IRON-RICH)	liver, kidney, heart, gizzard, intestines or other organ meats or blood-based foods. **Chuny, nyama rogno, obo, matumbo, remo gi mamoko.**	8 **(YES=1)** **(NO=2)**
9	FLESH MEATS	beef, pork, lamb, goat, rabbit, wild game, chicken, duck, or other birds. **Ring-dhiang, anguro, rombo,diel, apuoyo, le, gweno**.	9 **(YES=1)** **(NO=2)**
10	EGGS **Tong'**	All types	10 **(YES=1)** **(NO=2)**
11	FISH **Rech**	Fresh or dried fish or shellfish. **Manumo koso mothol; Omena, ngege, mbuta gi mamoko**	11 **(YES=1)** **(NO=2)**
12	LEGUMES, NUTS AND SEEDS	beans, peas, lentils, nuts, seeds or foods made from these. **Ng'or oganda, njugu, ndengu kata chiemo molos gi magi**	12 **(YES=1)** **(NO=2)**
13	MILK AND MILK PRODUCTS **chakgi**	milk, yogurt or other milk products	13 **(YES=1)** **(NO=2)**
14	OILS AND FATS **Mor tedo**	oil, fats or butter added to food or used for cooking	14 **(YES=1)** **(NO=2)**
15	SWEETS **Tamtam/peremende**	sugar, honey, sweetened soda or sugary foods such as chocolates, sweets or candies **sukari, mar kich, soda, chocolate,tamtam**	15 **(YES=1)** **(NO=2)**
16	SPICES, CONDIMENTS, BEVERAGES	Spices, black pepper, salt), coffee, tea alcoholic beverages e.g. beer, wine Or *local examples.***Apilo, chumbi, chach majani, chach kahawa,beer, busaa, chang'aa**	16 **(YES=1)** **(NO=2)**
	Individual level only	Did you eat anything (meal or snack) OUTSIDE of the home yesterday?	**(YES=1)** **(NO=2)**

HEDONISTIC SCALE – phase 2 – 2nd week

Client name:__/__/__/__/__/__/__/__/__/__/__/__/__/__/__/__/

Surv.No.Id.: __/__/

Group: (1) (2)

Place: (Kamaria = 1) (DSTV=2)

Questions

1.1. Ask them if they liked the _____ and circle their responses from the list below

☺		😐		☹
(very happy)	(happy)	(okay)	(Not happy)	(very unhappy)
1	***2***	***3***	***4***	***5***

1.2. Ask them what they think the _____ looks or taste like and record their response.

1.3. Ask them what it is that **they like about** the _____ and record their responses in the order they are given.

a. _____

b. _____

c. _____

d. _____

1.4. Ask them what they **do not like** about the _____ and record their responses in the order they are given

e. _____

f. _____

g. _____

h. _____

2. Make sure that by the end of the answers, they have given their opinion on each of the following aspects and record their assessment by circling a number on the scale of 1-5 below

	very happy	happy	okay	not happy	very unhappy
Colour	☺		😐		☹
	1	***2***	***3***	***4***	***5***
Taste	☺		😐		☹
	1	***2***	***3***	***4***	***5***
Sweetness	☺		😐		☹
	1	***2***	***3***	***4***	***5***
Texture	☺		😐		☹
(thickness/smoothness)	***1***	***2***	***3***	***4***	***5***

3. Write here any other comments made by the client that ***are not*** described above.

4. General comment

PATIENT QUESTIONNAIRE

[Acceptability TRIAL – Homa Bay – Valid International / MSF-F]

PART 1 - At admission

To fill by Valid International staff member:

1. Remember to the client that he/she could not qualify due to the criteria
2. No. of the MoH/MSF card: __/__/__/__/__/__/__/__/
3. First name: __/
4. **CRITERIA 1** - Age (years): __/__/
5. **CRITERIA 2 -** To be filled by MSF Medical staff member – possible clinical exclusion criteria

Presence of oedema	Yes/No
Adults with severe cerebral palsy or obvious dysmorphic features suggestive of an underlying syndrome (e.g. Trisomy 21) – excluding lipodistrophy	Yes/No
Amputated limbs (if occurring during the trial)	Yes/No
With general mental health problems (e.g. Down syndrome, etc.)	Yes/No
Any uncontrolled or untreatable systemic opportunistic infection at the time of study entry or irreversible oral problems that prevent adequate swallowing (NB: typical AIDS oral thrush would not be an exclusion criteria)	Yes/No
Name (capital letters) of MSF Medical Staff Member: _____ Signature: _____ Date: __/__/2008	

To fill by Valid International staff member:

CRITERIA 3 - Weight (kg): __/ , __/__/Height (meters): __/ , __/__/ **BMI (kg/m^2):** __/ , __/__/

(ONLY acceptable range: 18.5 – 19.9)

CRITERIA 4 - Village/Town of residence: __/__/__/__/__/__/__/__/__/__/__/__/__/__/__/ NB: H.Bay or very close!!!!

CRITERIA 5 - Under Antiretroviral drugs right now? __/ (no=1; yes=2) NB: he/she MUST be under ART!!!!!!

CRITERIA 6 - Did the patient give his/her informed consent given: __/ (no=1; yes=2) NB: consent SHOULD be given!Sex: __/ (Female=1; Male=2) If a woman, is the patient lactating? __/ (No=1; Yes=2)

Marital Status: __/ (Married=1; Not Married=2; Widower=3)

Phone number(s) for contact (if any): __/__/__/__/__/__/__/__/__/__/__/__/__/__/__/__/

Under Plumpynut in the past? __/ (No=1; Yes=2)

FUCHIA number: __/__/__/__/__/__/__/__/__/__/__/__/__/__/__/__/

IMPORTANT: assign the survey ID No. + Group + Client Responsible here beneath

PART 2 - GENERAL

	Monday 30/06/2008	Tuesday 01/07/2008	Wednesday 02/07/2008	Thursday 03/07/2008	Friday 04/07/2008	Monday 07/07/2008	Tuesday 08/07/2008	Wednesday 09/07/2008	Thursday 10/07/2008	Friday 11/07/2008
Weight (in kg)	__/__/, __/	__/__/, __/	__/__/, __/	__/__/, __/	__/__/, __/	__/__/, __/	__/__/, __/	__/__/, __/	__/__/, __/	__/__/, __/
MUAC (in cm)	__/__/, __/					__/__/, __/				
Did the patient come with a carer? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Presence of oral sores? – check! (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Presence of throat sores? – check! (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Does the patient manage to swallow? – make a test! (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Ho do you feel today? • Not hungry?=1 • Little hungry=2 • Hungry=3 • Very hungry=4	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Does the patient present any visible sign of illness? (No=1; Yes=2) NB: if Yes → report to Filippo	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/

PART 3 – 24 HOURS RECALL – sheet 1/2

Question: Koro adwa penji ka inyalo paro matin kuom gik motimore chakre nyoro kogwen nyaka sani, be inyalo yiena atim kamano? Now I am going to ask you to remember few things regarding what happened since yesterday at dawn until now, is that ok with you? NB: administer this questionnaire BEFORE the consumption of the product!

	Monday 30/06/2008	Tuesday 01/07/2008	Wednesday 02/07/2008	Thursday 03/07/2008	Friday 04/07/2008	Monday 07/07/2008	Tuesday 08/07/2008	Wednesday 09/07/2008	Thursday 10/07/2008	Friday 11/07/2008
Question 1: Chakre nyoro kogwen, be isewinjo koyo kata liet? Since yesterday morning at dawn did you feel any fever? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 2:Chakre nyoro kogwen, be isediewo? to ka ne odiewo, idhi e choo didi? Since yesterday morning at dawn did you have any case of liquid dhiarrea? If so, how many times did you go to the toilet approximately?	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/	Number of times: __/__/
Question 3: Chakre nyoro kogwen be isewinjo ka chuny lewi? Since yesterday morning at dawn did you feel any nausea? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 4: Be ise ng'ok chakre nyoro kogwen? Have you vomited since yesterday morning at dawn? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 5: Chakre nyoro kogwen,be isewinjo ka iyi obir? Since yesterday morning at dawn did you feel a sort of fullness of the stomach? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/

sheet 2/2

	Monday 30/06/2008	Tuesday 01/07/2008	Wednesday 02/07/2008	Thursday 03/07/2008	Friday 04/07/2008	Monday 07/07/2008	Tuesday 08/07/2008	Wednesday 09/07/2008	Thursday 10/07/2008	Friday 11/07/2008
Question 6: Chakre nyoro kogwen, be isewinjo ka iyi rami? Since yesterday morning at dawn did you feel pain at your belly? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 7: Chakre nyoro kogwen, be isebedo gi chandrwok mar golo muya? Since yesterday morning at dawn did you have problems like flatulence? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 8: Chakre nyoro kogwen, be dendi kamora amora no oili ma ok ni kare? Since yesterday morning at dawn did some parts of your skin unusually itching ? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 9: Chakre nyoro kogwen, be isebedo ki fuolo? Since yesterday morning at dawn did you have cough attacks? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 10: Chakre nyoro kogwen, be isewinjo gimoro mopogore kata nyien kata gimora amora ma diher nyisa? Since yesterday morning at dawn did you notice anything strange or new? (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question 11: Chakre nyoro	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/

	Monday 30/06/2008	Tuesday 01/07/2008	Wednesday 02/07/2008	Thursday 03/07/2008	Friday 04/07/2008	Monday 07/07/2008	Tuesday 08/07/2008	Wednesday 09/07/2008	Thursday 10/07/2008	Friday 11/07/2008
kogwen, be isemwonyo yien moro amora mag vitamins? Since yesterday morning at dawn did you take any vitamins pills? (No=1; Yes=2)										
Question 12: Chakre nyoro kogwen, be isemadho nyuka mi imiyo u gi MSF?(ma ok plumpy) Since yesterday morning at dawn did you take any fortified porridge provided by MSF? (NB: not the plumpynut!) (No=1; Yes=2)	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/

PART 4 - PRODUCT

250 g to give		Monday 30/06/2008	Tuesday 01/07/2008	Wednesday 02/07/2008	Thursday 03/07/2008	Friday 04/07/2008	Monday 07/07/2008	Tuesday 08/07/2008	Wednesday 09/07/2008	Thursday 10/07/2008	Friday 11/07/2008
1. Did you calibrate the scale before using it? (No=1; Yes=2)		__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
2. Did you take the tare of the container ? (No=1; Yes=2)		__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
3. Kind of product (Plumpynut=1; RUTFH=2)		__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
4. Time to start (hours : minutes)		__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/
5. Quantity given (in grams) - 250 grams	A	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/
6. Quantity left (in grams)	B	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/
7. Quantity wasted and/or spilled (in grams)	C	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/
8. Quantity eaten (in grams) **NB: D = A – B - C**	**D**	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/
Question: Be diher mondo omedi chiemo no icham ka? Do you wish to have an extra amount to eat here? (No=1; Yes=2)		__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
9. Time to finish (hours : minutes)		__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/	__/__/ : __/__/

PART 5 - WATER

250 ml to give		Monday 30/06/2008	Tuesday 01/07/2008	Wednesday 02/07/2008	Thursday 03/07/2008	Friday 04/07/2008	Monday 07/07/2008	Tuesday 08/07/2008	Wednesday 09/07/2008	Thursday 10/07/2008	Friday 11/07/2008
1. Brand of water (name)		<____>	<____>	<____>	<____>	<____>	<____>	<____>	<____>	<____>	<____>
2. Quantity given (in ml) 250 ml or more	A	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/
3. Quantity left (in ml)	B	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/
4. Quantity wasted and/or spilled (in ml)	C	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/
5. Quantity drunk (in ml) **NB: D = A – B - C**	**D**	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/	__/__/__/

PART 6 - FURTHER OBSERVATIONS / QUESTIONS

	Monday 30/06/2008	Tuesday 01/07/2008	Wednesday 02/07/2008	Thursday 03/07/2008	Friday 04/07/2008	Monday 07/07/2008	Tuesday 08/07/2008	Wednesday 09/07/2008	Thursday 10/07/2008	Friday 11/07/2008
The patient : • Refuses to continue = 1 • Is reluctant to continue = 2 • Accepts to continue but not very enthusiastic = 3 • Is eager to continue taking = 4	__/	__/	__/	__/	__/	__/	__/	__/	__/	__/
Question: Koro akwayo mondo ibed abeda thuolo mondo inyisa kaka iwinjo chiemo ma wamiyi ni? You can honestly express your opinion. How do you find the product? • **Ober** (Good) = 1 • **Omit ahinya** (Too sweet) = 2 • **Moo ng'eny** (Too oily) = 3 • **Chumbi ng'eny** (Too salty) = 4 • **Mit ahinya kendo moo ng'eny ahinya** (Too sweet & oily) = 5 • **Omit ahinya kendo chumbi ng'eny ahinya** (Too sweet & salty) = 6 • **Chumbi ng'eny kendo moo ng'eny ahinya** (Too salty & oily) = 7 • **Omit ahinya, chumbi ng'eny kendo moo ng'eny ahinya** (Too sweet & oily & salty) = 8	__/		__/		__/		__/		__/	
SIGNATURES OF THE RESPONSIBLE (for the client)										

9.3 Published articles

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A qualitative investigation of adherence to nutritional therapy in malnourished adult AIDS patients in Kenya

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Abstract

Objective: To understand factors affecting the compliance of malnourished, HIV-positive adults with a nutritional protocol using ready-to-use therapeutic food (RUTF; Plumpy'nut®).

Design: Qualitative study using key informant interviews, focus group discussions and direct observations.

Setting: Ministry of Health HIV/programme supported by Médecins Sans Frontièrs (MSF) in Nyanza Province, Kenya.

Subjects: Adult patients (*n* 46) currently or previously affected by HIV-associated wasting and receiving anti-retroviral therapy, their caregivers (*n* 2) and MoH/MSF medical employees (*n* 8).

Results: Thirty-four out of forty-six patients were receiving RUTF (8360 kJ/d) at the time of the study and nineteen of them were wasted (BMI $< 17\,kg/m^2$). Six of the thirteen wasted out-patients came to the clinic without a caregiver and were unable to carry their monthly provision (12 kg) of RUTF home because of physical frailty. Despite the patients' enthusiasm about their weight gain and rapid resumption of labour activities, the taste of the product, diet monotony and clinical conditions associated with HIV made it impossible for half of them to consume the daily prescription. Sharing the RUTF with other household members and mixing with other foods were common. Staff training did not include therapeutic dietetic counselling.

Conclusions: The level of reported compliance with the prescribed dose of RUTF was low. An improved approach to treating malnourished HIV-positive adults in limited resource contexts is needed and must consider strategies to support patients without a caregiver, development of therapeutic foods more suited to adult taste, specific dietetic training for health staff and the provision of liquid therapeutic foods for severely ill patients.

Keywords
HIV
Wasting
Supplementation
Ready-to-use therapeutic food

Undernutrition associated with HIV is a public health concern in Africa. Demographic and health surveys in eleven sub-Saharan countries estimated that 10·3% of HIV-infected women (aged 15–49 years) had a BMI $< 18{\cdot}5\,kg/m^2$[1]; data for men were not available. In urban Lusaka, Zambia, 9% of adults (3624 out of 40 778) started anti-retroviral therapy (ART) with a BMI $< 16{\cdot}0\,kg/m^2$[2].

Despite the increasing availability of ART, and patients enrolled in food programmes while on treatment reporting greater adherence to their medication[3,4], HIV wasting is still common. Although the beneficial effects of ART on severe malnutrition in adults are well documented, Carr[5] reported severe toxicity associated with ART in well-nourished individuals, and it has been suggested that side effects may be worse in malnourished individuals[6].

However, the relationship between nutritional status, therapy and survival of adults undergoing ART is controversial. According to Paton *et al.*[7], a BMI $< 17\,kg/m^2$ at the time of starting ART is associated with decreased survival in adults. A large observational study of patients receiving ART in Kenya and Cambodia (*n* 5069) showed that a weight gain of only 5% in 3 months increased survival in adults with a BMI $< 17\,kg/m^2$[8].

Bahwere *et al.*[9] reported that a novel ready-to-use therapeutic food (RUTF), nutritionally similar to commercially

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available paediatric RUTF, was acceptable to malnourished Malawian patients who were not receiving ART, and that it improved their physical activity performance, nutritional status and survival.

On the other hand, Ndekha *et al.*[10] found no difference in short-term survival when providing an energy-dense RUTF, or a lower-density porridge-based food, despite an increased weight gain with RUTF (*n* 450).

A retrospective analysis[11] of surveillance data on adults under ART (*n* 329) and with a BMI $< 17\,kg/m^2$, who were either receiving or not receiving an RUTF (Afya; Compact AS, Bergen, Norway), also reported that it was difficult to conclude a clear benefit of supplementary food in the early months of ART in terms of survival.

In 2007, the UN officially approved the use of RUTF for the treatment of acute malnutrition in children[12]. This approach has also been adopted in nutrition and health programmes in developing countries targeting adults with HIV/AIDS. However, only a paediatric formulation is commercially available and there is limited evidence for its efficacy, and little data on acceptability and adherence to this formulation in HIV/tuberculosis (TB)-positive adults.

To understand why nutritional support may not be providing consistent benefits, it is necessary to investigate, among other things, the compliance of patients to nutritional treatment and understand the factors that affect this. In the present paper, we use 'compliance' to describe the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds to agreed recommendations from a health-care provider[13–15].

The research questions of the present study aim (i) to understand and describe compliance with a protocol based on a specific RUTF (Plumpy'nut®; Nutriset, Malaunay, France) among malnourished adults living with HIV; and (ii) to determine any key barriers to compliance.

To our knowledge, the present study is the first to qualitatively investigate compliance with nutritional protocols based on RUTF that aim at rehabilitating malnourished HIV adults. We report the results according to the COREQ (consolidated criteria for reporting qualitative research) guidelines[16].

Experimental methods

The present research took place in Homa Bay, Nyanza Province, which is on the Kenyan side of Lake Victoria. In Kenya, in 2007, the prevalence of HIV was the highest in Nyanza Province (15·3 %), more than double the national prevalence estimate[17]. In January 2006, the non-governmental organisation Médecins Sans Frontières (MSF), France, introduced a nutritional rehabilitation programme for malnourished adults enrolled in the Ministry of Health (MoH) ART programme, Kenya, which utilised the most commonly available RUTF (brand name: Plumpy'nut®; 8360 kJ/d (2000 kcal/d) equal to four sachets of 92 g each). Adults (≥15 years of age) were considered malnourished (admission criteria) when BMI was $<17\,kg/m^2$ and/or middle upper-arm circumference (MUAC) was <185 mm and/or the presence of oedema was observed. Discharge criteria from the nutrition programme included BMI $\geq 18\,kg/m^2$ and MUAC ≥ 185 mm, and absence of oedema in at least two consecutive visits.

Along with the supply of RUTF, the medical staff provided generic nutritional counselling. These same staff members had never received any specific training in therapeutic nutritional treatment counselling for HIV adult patients.

Subjects recruitment and sampling

The study subjects, enrolled at the MoH/MSF HIV/TB programme in Homa Bay health district, Nyanza Province, Kenya, came from three groups: patients enrolled in the programme (some already nutritionally rehabilitated); their caregivers; and medical staff (counsellors, nurses and clinical officers). Patients <15 years of age were not admitted into the study group. The patients were recruited either at MoH/MSF HIV clinics A and B at Homa Bay hospital or from TB wards 7 and 8 of the same hospital.

The study followed a non-probabilistic, purposive, heterogeneous, non-proportional quota sampling system. Data saturation was achieved after approximately two-thirds of the study; however, recruitment continued along the entire planned period (3 weeks). During the study period, patients coming for their usual routine visit were invited to participate by the nurse in charge of the nutrition programme. All the health staff working at the clinic during the study agreed to participate. All focus group discussions and interviews occurred in a quiet area within the HIV clinic compound in the presence of researchers only, whereas direct observations were made in the TB multidrug resistance ward at Homa Bay hospital.

Data collection and data analysis

The research applied three qualitative methods and the results were triangulated. Focus group discussions involved patients and caregivers and one separate session with members of the MoH/MSF medical staff; semi-structured interviews were administered to patients on a one-to-one basis; direct unobtrusive observations were made of Plumpy'nut® distribution and consumption in the HIV/TB wards. The questionnaires and focus group discussions used a variety of techniques, including free listing, ranking exercises and open-ended questions (see footnotes in Table 3).

Questionnaires and focus group guides

Two guides were developed and piloted for use in the focus groups: one for patients and caregivers and one for the health staff members. The guides and questionnaires covered four topics: (i) information provided to patients about the recommended use and consumption of Plumpy'nut®; (ii) knowledge and attitude of patients about the role of

Plumpy'nut® in their therapy; (iii) dietary practices and Plumpy'nut® consumption; and (iv) patient's and caregiver's experience of the Plumpy'nut® distribution system.

A checklist for the direct observations was developed and covered the ways of consuming Plumpy'nut®, their advantages and disadvantages, together with the role of the caregiver.

All focus group discussions were recorded on tape, allowing the checking of information that was not clear from the written notes. The focus group discussions and interviews did not last for more than 1.5 and 1 h, respectively. The direct observation sessions lasted between 30 min and 1 h. A small number of photographs were taken with the informed consent of patients.

The research team and the relationship with subjects

The focus group discussions and interviews were conducted in the Luo language. Two native speakers, a female and a male, were recruited as interpreters and provided with 2 d training on the study and methods to be used. Time for familiarisation with the study guides was provided.

The principal researcher was a Caucasian male who was trained in public health nutrition at MSc level, and was not an MSF employee. He attended all focus group sessions and benefited from simultaneous translation by an interpreter. The principal researcher personally facilitated, in English, the focus group discussion with the health staff, and subsequently transcribed the recorded tape himself. Other discussions were facilitated by the study interpreters. The discussion transcript was not returned to the members for comments or corrections. All participants were provided with information about the study and assured that clinical services or RUTF provision would not be affected by refusal to participate.

Identification of common themes

The focus group discussion transcripts were manually coded by the principal researcher, highlighting keywords, key concepts and any minor or contradictory themes. Records of direct observations were reviewed and evidence summarised. Quantitative data from the interviews and the clinical and socio-economic profile of the focus group participants were entered in EpiInfo version 3·4·3 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and analysed in the STATA statistical software package version 8·0 (Stata Corp., College Station, TX, USA).

Detailed tables were prepared for each identified theme and its associated sub-themes. The theme tables contained separate columns referring to the evidence obtained on each theme using one of the three research methods. This allowed triangulation of evidence and comparison and discussion of the common themes that emerged. Following this process, the themes and sub-themes from the separate tables were compiled and overall conclusions drawn. Conclusions and associated recommendations were discussed with the health and management staff of the programme during a feedback process.

Results

From January 2008 to March 2009, MSF admitted 782 malnourished adults into the therapeutic nutrition programme; the monthly mean weight gain was 1·8 (SD 0·5) and 1·8 (SD 0·6) g/kg per d, respectively, for severely and moderately malnourished adults.

Study group characteristics

Table 1 provides descriptive data on the forty-six participating patients. Thirty-four were still under treatment with Plumpy'nut®. More than half of them were women and the average age was 33 years. All patients were married and the majority had their spouse still alive; twelve out of the forty-six patients were widowers. All subjects who were approached agreed to participate in the study and provided written informed consent.

Table 2 summarises the methods used and the number of patients, caregivers and health staff participants. Twenty-two current and ex-patients received one-to-one interviews and eighteen participated in focus group discussions. Six in-patients were directly observed. Two caregivers were recruited to participate in focus group discussions. Eight MoH/MSF employees participated in the focus groups with the medical staff (counsellors, nurses and medical doctors). None of the subjects were involved in more than one data collection method.

Table 1 Profile of participating patients (*n* 46)

Characteristic	Participants	
	n	%
Male	18	39
Female	28	61
Age (years)	33·3	
Married (missing records = 1)	45	100
Spouse alive	33	73
Widowers	12	27
Mean number of children (missing records = 1)*	3·0	
Serological status (missing records = 6)		
HIV positive	24	60
HIV/TB positive	16	40
Nutritional rehabilitation (missing records = 1)		
Enrolled into the nutrition programme at the time of the study		
No longer meeting admission criteria of malnutrition†	15	33
Meeting admission criteria of malnutrition‡	19	42
Discharged by the time of the study	11	25

TB, tuberculosis; MUAC, middle upper-arm circumference.
*Age not specified.
†BMI ≥ 17 kg/m^2 and/or MUAC ≥ 185 mm.
‡This group included thirteen out-patients and six in-patients. The in-patients were from the TB multi-drug resistance ward.

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Table 2 Summary of methods and participants

Methods	Participants (*n* 56)*
Individual interviews with current and ex-patients	22
Five focus group discussions from three to five participants, including:	
Current and ex-patients	18
Caregivers	2
Direct observations on individual in-patients and their caregiver's role	6
One focus group discussion with health staff	8

*None of the study subjects participated in more than one method.

Among the out-patients (*n* 13) who were still malnourished, six travelled to the clinic without a caregiver on the day of the study (two missing data). One walked, whereas the rest took public transport; the average time to reach the clinic was almost 2 h. The six in-patients recruited for the direct observations were found in the TB wards of Homa Bay hospital and they were all HIV positive; two of them were multi-drug resistant and their appetite might have been affected by their TB status and/or HIV status, plus by side effects of specific drugs.

Understanding compliance

The following sections summarise the key themes emerging from the analysis of the results. Only fourteen out of twenty-two interviewed patients reported complying with the prescribed amount of Plumpy'nut®.

Perceptions about Plumpy'nut®

Table 3 lists the aspects that may both enhance or decrease compliance with Plumpy'nut®, and were mentioned during the majority of focus groups and interviews. It was frequently reported that Plumpy'nut® can be 'associated with a drug' (same role and effect of a drug), 'brings (physical) strength' and 'allows to go back to work'. Increases in weight gain were reported and feelings of hunger said to decrease. Positive feelings about the use of the product can be summarised by the quote: 'ART is a drug to fight the infections, but does not give strength like Plumpy'nut® to go back to work'.

Turning to the negative perceptions of participants, some patients complained that the taste of Plumpy'nut® was responsible for nausea and vomiting. Participants also argued that the 'first 3 or 4 d are the most critical ones' and that 'after then, it becomes easier' to comply with the prescription. Among the patients interviewed, only one out of forty mentioned oral thrush as the main cause for low acceptability. In contrast, the health staff focus group voiced that the initial clinical conditions including swallowing capacity are crucial for patients' compliance. The interviewees provided suggestions about how to improve the product (see Table 3).

The medical staff expressed doubts about the role of Plumpy'nut® in promoting weight gain, since 'ART is far more important in severely malnourished patients'.

Sharing practices

Compliance was found to be closely linked with food-sharing practices. More than half (fourteen out of twenty-two) of the interviewed patients reported sharing Plumpy'nut® with children and other adults and this was confirmed by most focus groups. The medical staff was particularly concerned about the sharing practice at the community level, because of their observation that '…in the hospital wards, it is common'. In two of the focus groups, patients reported incidents of Plumpy'nut® trading or selling. This, however, seems to be limited to schoolchildren, because among adults the product was associated with HIV treatment and was thus potentially stigmatising. The majority of patients who declared that they tried to prevent sharing ('hiding the product in the closet from children'; '…or from adults') did so because Plumpy'nut® was considered part of the 'medical drug prescription'. Only one interviewee reported that Plumpy'nut® could be actually harmful for an HIV-negative person. One member of the medical staff suggested that Plumpy'nut® is so important for household food security that sharing represents a strategy to delay the moment of programme discharge.

Mixing Plumpy'nut® with other foods

Only one patient reported consuming Plumpy'nut® exclusively, whereas mixing Plumpy'nut® with other food was a common practice mainly with local staple starchy food (*ugali*), fresh vegetables, fish, rice, cereals, legumes, meat, cooked vegetables (*sukuma wiki*) and chapatti (in order of reported frequencies). Monotony of diet, nausea, vomiting or salty taste were the main reasons for mixing. Stirring Plumpy'nut® into hot water produces something that is similar to a popular, peanut-based, traditional food (*ogila*). Some others mentioned that 'once you start mixing the Plumpy'nut®, it is hard to go back and eat it alone'. Members of the medical staff suggested (contrary to programme recommendations) that patients with severe clinical conditions (e.g. oral thrush) should mix the Plumpy'nut® with tea.

Key barriers to compliance

Inability to transport ration

Physical weakness, absence of a caregiver during collection of supplies, cost of transport and stigma were key barriers to compliance. The prescribed supply of Plumpy'nut® per out-patient was monthly and weighed approximately 12 kg. A malnourished out-patient without a caregiver did not have enough strength to carry such weight. Therefore, the out-patients were invited to take half of the monthly ration and come back to collect the second half of the supply in 2 weeks' time. Health staff members reported that most patients could not afford to travel twice a month to the clinic. It can be speculated that these patients spread out the 2 weeks' provision along the entire month. This is consistent with the reports of many patients. No data could be collected on how many

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Table 3 Summary of key themes and sub-themes

Theme	Individual interviews	Focus group discussions*	Direct observations
Compliance with Plumpy'nut®			
● Only approximately half of the patients complied with the prescribed amount	X†	–	X
Positive aspects reported about Plumpy'nut® – participants think that:			
● It is similar to a drug rather than a food, in terms of both usage and role in recovery	X†‡	X	–
● It 'brings strength'	X†‡	X	–
● It 'allows to go back to work'	X†‡	X	–
● Increases weight gain	X†‡	X	
● Decreases the feeling of hunger	X†‡	X	–
● Has a smell and packaging that are well accepted	X†‡	X	X
● Offers the possibility to mix it with other food and therefore reduce:	X†‡	X	X
○ diet boredom	X†	X‡§	–
○ nausea	X†	X‡§	X
Negative aspects reported about Plumpy'nut® – participants think that:			
● It can cause nausea and vomiting	X†‡	X	X
● The first 3–4 d of consumption are crucial for compliance, becoming easier later	–	X	X
● The taste is:			
○ too sweet	X†‡	X‡§	–
○ too oily	X†‡	X‡§	–
○ too salty	X†‡	X‡§	–
● Consistency should be more liquid or like a biscuit or a powder (milk powder)	X†‡	X	–
● It comprises a monotonous diet, leading to boredom	X†‡	X	–
Sharing Plumpy'nut® with both other adults and/or children is a common practice	X†	X	–
Reasons for sharing:			
● Food insecurity in the household	–	X‡	–
● Children like it	X†‡	X‡	–
● The partner or relative is ill and/or HIV positive but not malnourished (energy booster)	–	X‡	–
Mixing Plumpy'nut® with foods is a common practice	X	X	X
Reasons for mixing:			
● To reduce monotony of the diet	X†‡	X‡	X
● To reduce nausea, vomit, salty taste	X†‡	X‡	X
● Because the Plumpy'nut® has separated into oil and solid phases	X†‡	–	–
● Because Plumpy'nut® with water reminds participants of a traditional food	–	X‡	–
● Because it was suggested by the health staff	–	X‡	–
Knowledge and attitudes of medical staff			
Medical staff expressed doubts about the positive role played by Plumpy'nut® in nutritional rehabilitation; ART was perceived as being much more important	–	X	–
Patient counselling			
● Counselling messages focus on:			
○ human nutrition (e.g. 'proteins are available in meat, eggs and cheese')	X†‡	X‡§	–
○ improvement of general conditions when consuming Plumpy'nut® (weight gain, appetite, strength)			
● Most patients did not know the relationship that exists between HIV infection, their thinness and their ART therapy	X†‡	X‡	–
● Staff declared that they did not know what counselling to provide to patients with severe clinical conditions (e.g. oral thrush)	X†‡	X‡	X
● Most patients do not receive routine information about why, when and how to consume Plumpy'nut®; when this happens, it comes from the individual initiative of the health staff	X†‡	X‡	X
Distribution system for Plumpy'nut®			
● Half of the patients still under nutritional rehabilitation come to the HIV clinic without a caregiver	X†	X	–
● The patients cannot carry more than a 2 weeks' supply of Plumpy'nut® (~6 kg) instead of the whole month's supply	X†	X	X
● The appointment schedule for ART or clinical check-ups is monthly in most cases; therefore, patients or caregivers do not come back to collect the missing 2 weeks' supply of Plumpy'nut®	X†	X	–
● Very weak patients are in absolute need of the caregiver even to open the sachets, to mix it with other food (when needed) and consume it	–	–	X
● Bulky supply (6–12 kg) and branded container (box) are very noticeable and associated with stigma within the community	X†	X	X

ART, anti-retroviral therapy.
*The focus groups involved either patients together with caregivers (five groups, with three to five participants) or health staff members (one group with eight participants).
†Tool used: closed and/or open questions.
‡Tool used: free listing.
§Tool used: ranking exercise to select the main themes reported here.

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patients came back to collect the missing mid-month supply or the relationship with defaulting and survival.

Stigma associated with therapeutic foods

In a region where HIV-related secondary malnutrition is common and treated with Plumpy'nut®, this product has become strongly associated with HIV. For this reason many patients were reluctant to walk home with boxes reading the brand name (Plumpy'nut®). One patient said 'I can disguise the ART tablets saying that they cure something else, but I cannot disguise Plumpy'nut® because a month's supply is too bulky and visible'.

Clinical status and role of the caregiver

Among the in-patients who were directly observed, all patients with a severe clinical condition could not comply with the prescribed amount. Two of them died during the course of the study. Alternative therapeutic diets, such as therapeutic liquid milk (formulas F75 and F100), the intake of which may have been easier for severely ill patients, was not available.

It was reported and observed that in-patients in the ward with the most severe clinical conditions can consume Plumpy'nut® only if mixed with other suitable food (e.g. water or porridge). This requires assistance from the caregiver. Patients with severe clinical conditions were so weak that they did not have sufficient strength even to open the sachet and mix the product with food.

Discussion

The present study has indicated that compliance with therapeutic feeding within this HIV programme is likely to be low. We have identified a number of issues that may reduce the consumption of RUTF to below the prescribed level. Although the nature of the study setting might have affected the patients' response, some of the findings are likely to be generalisable to other HIV and adult nutrition programmes that use this specific therapeutic food and a similar nutritional protocol.

The present study identified two groups of factors that limit specifically an RUTF-based protocol compliance: (i) factors directly related to the product design and (ii) factors related to programme design.

Factors related to product design

Although widely used for other patient groups, it is important to note that Plumpy'nut® was designed for treating severe acute malnutrition in children. There is evidence[18] to suggest that reported symptoms such as nausea and vomiting when consuming RUTF could be related to the drug treatment too. The taste of Plumpy'nut® was not considered suitable by many adult patients and therefore they often reduced intake or mixed it with other food. This practice may compromise the efficacy of RUTF by reducing overall energy and nutrient intake and delaying nutritional rehabilitation.

Despite the problems of taste and consistency acceptability, the results of this research suggested that most patients valued the nutritional therapy provided by Plumpy'nut®. Their attitude towards the product was more positive than that of most medical employees, perhaps because of lack of staff training on the anticipated benefits. However, the interviewed patients would reduce the sweetness (somebody suggested the addition of lemon juice), and would like to change the consistency into something 'more liquid' or 'into the form of a biscuit' or powder. Rarer comments mentioned included suggestions for improving the packaging, such as 'the sachet packaging should be replaced with ice-cream cup with lid'.

Factors related to programme design

Certain problems in accessing and consuming the therapeutic food were accentuated by the design of the overall programme and inappropriate staff training. Patients were not informed about how to correctly consume the RUTF. For example, counselling messages inappropriately advised adding the RUTF to tea and advised feeding strategies that were not feasible for the patient. Advice to consume RUTF at meal times (3 times/d) and/or together with ART drugs was not conducive to ensuring adequate intake. Some of the patients admitted that they disregarded such advice because of the 'strong' – difficult to eat – nature of the product, their bad clinical conditions combined with ART side effects (lack of appetite, nausea, vomiting, etc.). More appropriate advice would have been that based on therapeutic feeding guidelines[19] and should have recommended having small bites of RUTF throughout the day until the daily prescription of sachets was consumed. Box 1 presents the most common questions expressed by

Box 1

During dietetic counselling* sessions, the topics to be covered should respond to the following questions expressed by patients during the study: What is Plumpy'nut® (food/drug; composition)? Who is supposed to use it? What are its components? How often should I eat it along the day? What should I do when I do not manage to eat it because of nausea, vomiting or lack of appetite? Could I mix it with other foods? What should I avoid to drink or eat together with Plumpy'nut®? What are the consequences if I share my ration of Plumpy'nut® with other persons? Is it good for somebody who is not HIV positive to eat Plumpy'nut®? Is it good for somebody who is not thin to eat Plumpy'nut®? When should I stop eating Plumpy'nut®? Will I become thin again when I stop eating it?

*For an example of dietetic counselling material for HIV therapeutic feeding in adults, contact filippo@validinternational.org.

patients during the present study. The same questions lead to key counselling messages.

Frail patients who came to a clinic appointment without a caregiver sometimes ended up losing half of the prescribed RUTF supply, as they were unable to transport the food to their home. The situation could be improved by re-design of the distribution system, perhaps involving community-based organisations to support home-based care. Their importance is recognised in many HIV and nutrition interventions and protocols[20–24]. The health programme also needed to acknowledge and address the stigma factor attached to Plumpy'nut®. This could involve the use of anonymous packaging.

In case of extremely frail patients, the caregiver played a fundamental role in trying to overcome key barriers for compliance, such as simply opening the sachets or mixing it with other foods.

Main limitations of the present study

The present research did not correlate the collected data with clinical information such as patients' survival, CD4 count, weight gain or BMI changes that might have helped in understanding the impact of such a programme in the presence of household/community sharing, food mixing, lack of counselling and clinical difficulties in swallowing among others.

The present research did not aim to understand the link between nutritional therapy and ART compliance. RUTF is meant to be used in out-patient programmes, but the present study was restrained by lack of observations at the community level.

The two study interpreters were not only employed as health promoters in the MoH HIV programme but were also clients of the MoH/MSF HIV/TB programme. One of them had been previously successfully rehabilitated in the nutritional programme. Therefore, they might have previously met some of the patients enrolled in the study and/or developed specific perceptions about the topic, introducing possible bias.

Conclusions

Overall, the research suggests that training and information material is needed to ensure that medical staff can support the patient to overcome the first most crucial phase of the treatment. The very first contact with the patient should include a test to assess the swallowing capacity. Reduced capacity to swallow is common and it may imply a lower compliance with nutritional therapy and an increase in mortality risk. Consistent with the community-based management of malnutrition approach, medical staff should ask the patient to consume some amount of RUTF in his presence to verify his swallowing capacity. According to the results of this test, dietetic solutions must be discussed and agreed upon together with the patient and the caregiver when present. Patients who are unable to swallow at all should be hospitalised and treated according to the in-patient nutritional therapeutic protocol developed by WHO[25], which utilises milk-based liquid therapeutic nutritional products such as F75 and F100.

The study showed that Plumpy'nut®, designed for malnourished children, needs improvement to meet the palatability preferences expressed by adult patients. A reduction in the perception of sweetness and fat components was solicited by the patients. However, any HIV/TB therapeutic nutrition programme should not introduce newly designed RUTF until positive clinical results have been demonstrated.

Further studies more closely correlating compliance and recovery rates are likely to improve the perception of medical staff towards the effectiveness of this kind of programme, possibly improving their performance as well.

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Methodology and Mathematical Modeling

Low-Cost, Ready-to-Use Therapeutic Foods Can Be Designed Using Locally Available Commodities with the Aid of Linear Programming[1,2]

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Abstract

According to the United Nations (UN), 25 million children <5 y of age are currently affected by severe acute malnutrition and need to be treated using special nutritional products such as ready-to-use therapeutic foods (RUTF). Improved formulations are in demand, but a standardized approach for RUTF design has not yet been described. A method relying on linear programming (LP) analysis was developed and piloted in the design of a RUTF prototype for the treatment of wasting in East African children and adults. The LP objective function and decision variables consisted of the lowest formulation price and the weights of the chosen commodities (soy, sorghum, maize, oil, and sugar), respectively. The LP constraints were based on current UN recommendations for the macronutrient content of therapeutic food and included palatability, texture, and maximum food ingredient weight criteria. Nonlinear constraints for nutrient ratios were converted to linear equations to allow their use in LP. The formulation was considered accurate if laboratory results confirmed an energy density difference <10% and a protein or lipid difference <5 g · 100 g^{-1} compared to the LP formulation estimates. With this test prototype, the differences were 7%, and 2.3 and −1.0 g · 100 g^{-1}, respectively, and the formulation accuracy was considered good. LP can contribute to the design of ready-to-use foods (therapeutic, supplementary, or complementary), targeting different forms of malnutrition, while using commodities that are cheaper, regionally available, and meet local cultural preferences. However, as with all prototype feeding products for medical use, composition analysis, safety, acceptability, and clinical effectiveness trials must be conducted to validate the formulation. J. Nutr. 142: 955–961, 2012.

Introduction

Since 2007, the United Nations (UN)[5] (1) has recommended the use of ready-to-use therapeutic food (RUTF) at the community level for the treatment of pediatric severe acute malnutrition (SAM) in low-income countries (1). The reason is that RUTF does not require any preparation or addition of water before ingestion, can be stored for long periods without refrigeration, allows individual packaging, and can therefore be used effectively in situations with nonoptimal hygiene conditions (2). Moreover, RUTF meets the specifications for type I and II micronutrient densities (1,3) that have been found to contribute to effective management of SAM in children (3). A classification of this range of products is available elsewhere (4). Plumpy'nut is the most common commercial brand that has been clinically trialed so far (5,6), but an increasing number of therapeutic products are being tested.

RUTF is not always available where needed. India alone counts 8 million SAM children (7) in need of nutritional rehabilitation (8), yet it has not been possible to legally import RUTF from Europe since 2009. In this and other countries, the relatively high cost of Western brands and local policies have prevented the widespread importation of RUTF, boosting the demand for regionally appropriate solutions (9).

The market for products to use in feeding programs is large. The World Bank estimates that each year, ~$6.2 billion are needed to treat 3.5 million children <5 y of age affected by SAM or moderate acute malnutrition (10). If not treated on time, these might represent more than one-third of all pediatric deaths worldwide (10). A large coalition of international institutions is currently engaged in raising the needed funds (11).

However, some aspects of therapeutic feeding still require more evidence-based understanding. The current RUTF formulation is based on results from a limited number of studies, in a few settings, showing rapid weight gain (12). Consequently, in other settings, with different underlying nutrient deficiencies and infectious disease profiles, similar weight gains would perhaps occur, with nutrient levels different from those in use (13–16).

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[2] Author disclosures: F. Dibari, E. H. I. Diop, and S. Collins (Director) work for Valid Nutrition. Valid Nutrition is involved in trialing, manufacturing, and marketing the ready-to-use foods described in this paper. A. Seal, no conflicts of interest.
[5] Abbreviations used: DV, decision variable; FCD, food composition database; LP, linear programming; OF, objective function; PDCAAS, protein digestibility–corrected amino-acid score; RUF, ready-to-use food; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; TFD, true fecal digestibility; UN, United Nations; WFDAS, World Food Dietary Assessment System.
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The current commercial formulation of RUTF is not acceptable to all the patients in need of therapeutic nutrition in developing countries. A study reported that adult HIV-positive wasted patients in Africa struggled to comply with the current RUTF-based treatment (17). The same study recommended improving the formulation to meet the tastes of the beneficiaries and increase its acceptability.

Evidence-based nutrition research ideally relies on costly randomized clinical trials. Therefore, a robust method is required to design the trial RUTF before randomized clinical trial implementation. At present, there is no internationally endorsed protocol to design products of this kind.

A design method based on linear programming (LP) can help in the development of novel RUTF and other products with similar properties, termed here ready-to-use foods (RUF). LP analysis is an operational research approach that is used to model complex multifactorial problems, including diet-related ones (18). Since 1959 LP has been applied to human nutrition (19) and since 1983, also to diet planning for developing countries (20). More recently, with the aid of specific software, LP was used for complementary feeding programs (21) or in the design of diets for specific populations (22,23). LP is also used to design personal diets, define institutional nutritional practices, support decision-making in nutrition education or agricultural programs, define food fortification activities, and undertake analysis of economic constraints on human diets (22–24). LP can be used for assessing the economic value of fortified food supplements (25) and in predicting limiting nutrients in specific diets (21).

LP is a suitable decision tool for designing novel food-based formulations. The method helps by identifying the cheapest possible combination of food ingredients that meet a set of nutritional requirements (20,23,26), avoiding a "trial and error" approach (21,27).

The objective of this study was to test a LP-based method for designing the cheapest formulation of a RUF that fulfils predefined macronutrients requirements by using region-specific foods that are culturally acceptable and can be processed with locally available technologies. To our knowledge, this is the first study describing how LP can be used to design RUF. The study should be of interest to international nutritionists and food technologists involved in designing novel RUF.

Materials and Methods

Developing a LP model for RUTF

LP is a tool to optimize (minimize or maximize) a linear objective function (OF) while respecting multiple linear equality and inequality constraints (21). When used for selecting the lowest cost diet/formulation, the OF can be expressed in the following form (22):

$$Y = k_0 + k_1W_1 + k_2W_2 + \ldots + k_nW_n,$$

where Y is the cost, k_1, k_2… k_n are constants, equivalent, for instance, to the cost per unit weight for food ingredients F_1 to F_n, and W_1, W_2,…W_n are the decision variables (DV), i.e., the weights of foods F_1, F_2…F_n in grams. The usual aim will be to minimize the cost of the formulation (Y) by changing the weight of the different ingredients while meeting a range of different constraints. These mathematical constraints (equality, greater than, or less than) are imposed on one or more of the DV (W_1, W_2,…W_n) to ensure that the nutrient content of the product meets design requirements and does not exceed upper thresholds. A LP solution is feasible when all its constraints are achievable. When the highest possible concentration of a nutrient is less than a minimum constraint, when the lowest concentration of a nutrient is higher than a maximum constraint, or an equality constraint cannot be respected, the model is considered unfeasible (16,18). Constraints in food formulation problems may be linear or nonlinear, but LP can be applied only when all the constraints are linear (22). A constraint is considered linear when it can be expressed in the following way:

$$\begin{aligned} k_1W_1 + k_2W_2 + \ldots + k_nW_n &\geq a_0 \quad \text{or} \\ k_1W_1 + k_2W_2 + \ldots + k_nW_n &\leq b_0 \quad \text{or}, \\ k_1W_1 + k_2W_2 + \ldots + k_nW_n &= c_0 \end{aligned}$$

where a_0, b_0, and c_0 are constants. Models including nonlinear constraints may have several solutions (local optimums) depending on the initial values and cannot be solved using LP.

In this study, we transformed nonlinear nutrient ratio constraints, such as the proportion of energy coming from protein, the proportion of energy coming from fat, and the proportion of energy coming from (n-3) and (n-6) fatty acids, into equivalent linear constraints. For example, the UN specifications for RUTF require that the proportion of total energy (E) coming from protein is >0.10 and <0.12 (1). This was expressed in the following nonlinear form:

$$(P_1W_1 + P_2W_2\ldots + P_nW_n)/(E_1W_1 + E_2W_2\ldots + E_nW_n) \geq 0.10 \text{ and } \leq 0.12$$

where P_1, P_2,…P_n and E_1, E_2,…E_n represent, respectively, the energy content from protein and the total energy content (kJ) in W_1, W_2,…W_n (g) of each food ingredient F_1, F_2…F_n. Therefore, the protein:energy constraint (C) was expressed as a linearized function of the weight of different foods:

$$W_1(P_1 - 0.10E_1) + W_2(P_2 - 0.10E_2)\ldots W_n(P_n - 0.10E_n) \geq 0$$

and

$$W_1(P_1 - 0.12E_1) + W_2(P_2 - 0.12E_2)\ldots W_n(P_n - 0.12E_n) \leq 0$$

Some authors (21) suggest avoiding nonlinear constraints wherever possible because of their complexity. Therefore, we avoided including more complex nonlinear constraints in the formulation such as protein quality expressed as protein digestibility-corrected amino-acid score (PDCAAS) (28) and true fecal digestibility (TFD) (28,29). However, these 2 parameters were calculated and manually assessed in the final model.

In this study, the OF consisted of identifying the lowest price given by the sum of each food ingredient cost (C_1, C_2,…C_n) multiplied by the DV (food weights: W_1, W_2,…W_n) while respecting the predefined constraints. Other definitions and graphic illustrations of LP theory are available elsewhere (16,18,20–22,26).

An example of a RUTF formulation optimized by LP

To explore the use of LP, we used it in the process of formulating a prototype RUTF that could be used in both adult and pediatric therapeutic feeding programs in East Africa and could be manufactured from locally available commodities. Such a product would yield considerable reductions in the logistic complexity and costs in large humanitarian operations.

The overall design, manufacture, and testing of the RUTF consisted of 4 phases (**Fig. 1**). The preliminary stage A involved identifying the target group and the desired composition of the prototype product. Potential food ingredients, nutrient composition, and price data were then identified and compiled. The DV, constraints, and OF for the LP model were defined and used in step B to set up and solve the LP model using Microsoft Excel (version 2007) and the Solver add-in. Phase C consisted of assessing the sensitivity of the optimized model and then manufacturing a small-scale test batch of the RUTF prototype to check the texture and compare the calculated composition with laboratory-based results. In phase D, safety and acceptability tests were conducted with the unfortified product. At the same time, the fortificant premix was designed, added, and its shelf life monitored. Soon after, clinical trials were used to validate the prototype formulation. Results from phase D will be reported elsewhere.

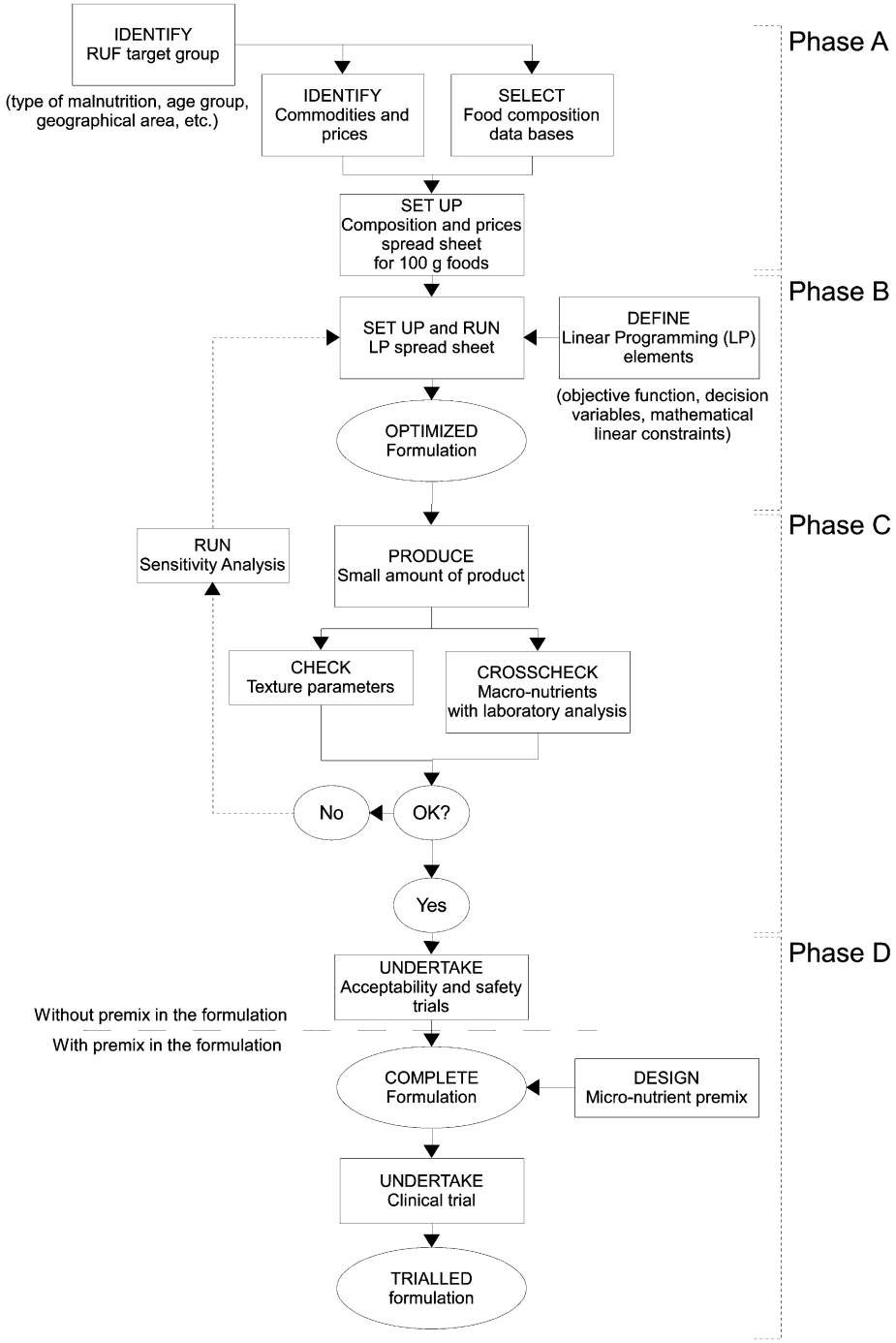

FIGURE 1 Proposed design and validation method for novel RUF. RUF, ready-to-use food.

Phase A: FCD and food prices

Choice of the FCD. The validity of the LP-optimized prototype formulation depends on the accuracy of the food composition database (FCD). The FCD sources were selected by using the following criteria: *1*) the widest representation of commodity composition data from around the world; *2*) the largest number of nutrient data values per food; *3*) food descriptors matching the selected ingredients; and *4*) internationally respected datasets, ideally with methods cited in peer-reviewed journals.

Choice of the food ingredients. Initially, one of the largest East African food aid manufacturers (Insta Products EPZ) identified one specific commodity for each of 4 preselected food categories: cereals, sugar, and oil.

Most East African capitals host extrusion industrial units for precooking and milling of cereals and/or pulses blends. In mixes of preground pulses and cereals, the correct application of extrusion processing achieves levels of starch gelatinization sufficient for digestion (30) while destroying most antinutritional factors (30).

Phase B: Setting up and running the LP model

The design of the RUTF had to respect several prestated conditions, which were derived from specifications for this class of product and from experience gained in the design of similar products. Four groups of constraints were considered: energy and nutrient concentration, palatability, texture, and total food ingredient weight. The linear and linearized nutrient concentration constraints that were applied are listed in **Table 1**.

TABLE 1 Components of the LP model and prototype RUTF formulation

	Initial target requirements	Optimized solution
OF, cost minimization, *$*	NA[1]	0.07
DV: weights of the selected foods[2]		
Soybeans, *g*	NA	31.9
Maize, *g*	NA	15.3
Sorghum, *g*	NA	7.0
Oil, *g*	NA	27.3
Sugar, *g*	NA	15.5
Constraints		
Energy and nutrients		
Energy, *kJ/100 g*	2174.0–2299.0[3]	2169.0
Protein energy/total energy[4], *%*	10.0–12.0	10.0
Fat energy/total energy[4], *%*	45.0–60.0	60.0
(n-3) Fatty acid energy/total energy[4], *%*	0.3–2.5	0.9
(n-6) Fatty acid energy/total energy[4], *%*	3.0–10.0	10.0
Palatability		
Sugar (sweetness), *g/100 g*	15.0–18.0[5]	15.5
Sorghum (taste improvement), *g/100 g*	7.0–10.0	7.0
Texture-related		
Fat content, *g/100 g*	28.0–36.0	34.6
Maximum food ingredient weight		
Final total weight, *g*	97.0	97.0
Monitored variables (not included as constraints)		
Quality of protein expressed as PDCAAS,[6] *%*	75.0–89.0[7]	85.7
TFD,[8] *%*	NA	83.0
Limiting amino acid	NA	Lysine

[1] The cost of the currently available product (Plumpy'nut) is ~$0.50/100 g when delivered in East Africa, at the time of this study. The reference includes costs such as manufacturing, transport from Europe, packaging, and import taxes. All the figures refer to 100 g of product. DV, decision variable; LP, linear programming; OF, objective function; PDCAAS: protein digestibility-corrected amino acid score; RUTF, ready-to-use therapeutic food; TFD, true fecal digestibility.

[2] Soy descriptor: soy flour full fat, raw [USDA SR20 (36)]. Maize descriptor: maizemeal, wholegrain, white [FAO-Minilist (33); item code CF00096]. Sorghum descriptor: sorghum, decorticated, flour [FAO-Minilist (33); item code CF00154]. Palm oil descriptor: oil, vegetable, palm [USDA SR20 (36)]. Sugar descriptor: sugar, white, cane, or beetroot [FAO-Minilist (33); item code SF00168].

[3] The UN specification is 2174 kJ · 100 g^{-1} (1). The constraint was relaxed to 2169 kJ · 100 g^{-1} to achieve a feasible LP solution.

[4] The constraint formulae were converted to a linear form as described in ''Methods.''

[5] The available literature (31) on pediatric RUTF reports a sugar content of 28 g · 100^{-1}. The constraint range was reduced to 15–18 g to make it more suitable for wasted adults living with HIV/TB [based on (17)].

[6] From (28).

[7] Calculation of PDCAAS based on (1,31,44) and using food composition data from (34,35).

[8] TFD coefficient calculated using the following foods (and descriptors): maize (corn, extruded cereal), soy (soy flour), sorghum (sorghum, cooked) (28,29).

Energy and nutrient concentration constraints. LP constraints were introduced to ensure that the RUTF formulation met the UN 2007 standards (1) for energy density and the ratios of protein, fat, and essential fatty acids to energy (Table 1).

Palatability-related constraints. Palatability constraints are common in dietary LP (21) and aim to avoid the creation of unacceptable tastes. In a study (17) looking at compliance with the current commercially available pediatric RUTF, HIV/TB-wasted Kenyan adults voiced the need for a reduction of the current sugar content (28%) (31). Lower sugar density was also shown to be acceptable to <5-y-old Zambian children in another preliminary study (personal communication, Abel Hailu, Valid Nutrition). Therefore, the sugar content was constrained to 15–18% (Table 1).

Sorghum improves the taste of extruded pulses/cereals blends, even if present in a small amount (personal communication, Stuart Allison, Insta Products EPZ). We introduced a minimum constraint of 7–10% for sorghum (Table 1) based on work with preliminary formulations.

Texture-related constraints. Texture-related constraints aim for a specific consistency in the food mix. RUF must have a paste-like property in order to be squeezed into the mouth by the adult and children patients, or by their caregivers. Therefore, a fluid consistency was not suitable. A texture similar to a biscuit can produce choking in children (32) and therefore was also considered unacceptable. A solid phase particle size <200 microns (31) and a fat range of 28–36% generally lead to a suitable paste texture during preliminary tests. The latter criterion was included as a constraint in the LP model (Table 1).

Total food ingredient weight constraint. Once the RUF is shown to be acceptable and safe (Fig. 1), a premix of vitamins and minerals is added to the formulation (phase D). The weight of the food ingredients therefore needs to be constrained to allow sufficient space for inclusion of the vitamin and mineral fortificant in the finalized product. Calculations indicated that up to 3% of the final product weight might be required for the premix. We therefore used an equality constraint to fix the weight of the RUTF food ingredients at 97 g (Table 1).

LP model and the software. The process of running the LP model consisted of: *1*) creation of the data layout on a Microsoft Excel spreadsheet; *2*) activation of add-in Solver Function, which is supplied with standard installations of Excel; *3*) assignment of the OF, DV, and constraints; *4*) running the LP procedure to solve the OF; and *5*) a sensitivity analysis. Steps 1–3 were applied following the procedure suggested elsewhere (21).

Phase C: comparison with laboratory results and sensitivity analysis

Comparison of FCD-based figures with the results from laboratory-based analysis. The Kenyan manufacturer (Insta Products EPZ) produced the prototype RUTF formulation in small batches and a local laboratory (Polucon Services Limited) performed the analysis (in triplicate) of the total energy, protein, and fat contents (**Table 2**). LP estimates, based on the FCD figures, were defined as acceptable when the difference in relative energy density was <10% and the difference in both protein and lipid densities were <5 g · 100 g^{-1}. Both differences were prestated and based on cutoffs used in food technology practice.

Sensitivity analysis. Sensitivity analyses reported by the Solver Function (see **Table 3**) were used to quantify how much ingredient costs and formulation constraints can vary without requiring a change in the values of the LP DV. This can be useful if ingredient costs are likely to vary and decisions need to be made about when to consider reformulation.

Results

The FAO-Minilist (33) was the first choice as the FCD source, because it fulfilled most of the selected criteria. FAO-Minilist, downloaded from the Nutrisurvey Web site (34), is a selection from the larger World Food Dietary Assessment System (WFDAS) database (35). The WFDAS is based on data from 6 countries from East, West, and North Africa, Central America, and South and Southeast Asia. All these areas are affected by malnutrition and are therefore of interest for the goal of this study. Other published studies have used the WFDAS dataset for LP dietetic purposes (16,21). FAO-Minilist and WFDAS included phytate among the antinutrients, although relevant nutrients, such as (n-3) and (n-6) fatty acids, were missing. Therefore, we added values for these nutrients from the USDA SR20 and Nutrisurvey databases (34,36).

Maize, soy, sorghum, palm olein oil, and sugar were the chosen commodities. Nutrients for maize (descriptor for this and

TABLE 2 Comparison of the LP-optimized model and the laboratory composition analysis of the same formulation

	Calculated nutrient densities[1]	Laboratory results[2]	Absolute difference	Relative difference
	A	B	B − A = C	(C/A) x 100
Energy kJ/100 *g*	2169.0	2235.0	66.0	3.0
Protein g/100 *g*	13.0	15.3	2.3	17.7
Protein energy/total energy	0.10	0.11	0.01	—
Lipid g/100 *g*	34.6	33.6	−1.0	−2.9
Fat energy/total energy	0.60	0.56	−0.04	—

[1] Sources of food composition (34,35). LP, linear programming.
[2] Methods applied (parameters, other information): Pearson (energy); Gafta May 91 (protein, Nx6.25%; lipid). By Polucon Services Limited, Msaada Avenue, Mombasa, Kenya; test report no. 2008/1282.

the other commodities are listed in the footnote in Table 1), sorghum, and sugar were obtained from FAO-Minilist (year of release not specified). Data for soybeans and palm olein oil were selected from USDA SR20 (released in 2009), because their descriptors were closer to the available commodities. However, lysine and tryptophan in soybeans data from USDA SR20 were, respectively, 27 and 58% higher than in the WFDAS data. The prices of maize, soy, sorghum, oil, and sugar were 0.30, 0.60, 0.30, 1.20, and $\$0.70 \cdot kg^{-1}$ respectively.

The final price of the formulation was $\$0.70 \cdot kg^{-1}$. The initial minimum energy density constraint ($2174\ kJ \cdot 100\ g^{-1}$) was manually relaxed by 0.2% ($2169\ kJ \cdot 100\ g^{-1}$) to achieve a possible solution (Table 1). All the resulting ratios between energy from protein (0.10), from fat (0.60), and from (n-3) and (n-6) fatty acids (0.009 and 0.10, respectively) and the total energy content matched the UN standards (Table 1). The quality of the protein (PDCAAS: 85.7%; TFD: 83.0%; lysine was the limiting amino acid) was close to the upper level of the reference range (75–89%). PDCAAS and TFD specifications and descriptors are included in Table 1.

The total energy in the LP model was 3.0% lower than in the laboratory-based figures. The protein and lipid contents estimated with LP were 2.3 and $1.0\ g \cdot 100\ g^{-1}$, respectively, lower and higher than the contents measured in the sample (Table 2).

Discussion

The method described above was used to successfully design a prototype RUTF formulation for the rehabilitation of HIV/TB-wasted adults and children <5 y with SAM in East Africa. The safety and acceptability of the prototype RUTF was subsequently confirmed in a trial (F. Dibari, P. Bahwere, H. Huerga, A. H. Irena, V. Owino, S. Collins, A. Seal, unpublished data).

Today, LP can be easily applied, whereas, historically, it received relatively little attention, perhaps because computers were not widely available when LP was first conceptualized and disseminated (22). The example illustrated in this paper was implemented using widely available software (Microsoft Excel Office 2007 and the Solver add-in). Other proprietary software, specifically designed for nutritional use and including LP functions, are also available, namely Microdiet (37) and Nutrisurvey (34).

In our study, laboratory analysis confirmed that the energy, protein, and lipid values of the prototype formulation were within the preestablished cutoffs, before and after that the energy constraint was relaxed (0.2%) (Table 2). The relative difference in the energy density (3%) was below the threshold of 10% and the protein and lipid absolute differences (2.3 and $1.0\ g \cdot 100\ g^{-1}$, respectively) were lower than the limit of $5\ g \cdot 100\ g^{-1}$. However, the relative difference in protein was large (17.7%). This was not surprising, because it is known that protein content, in particular from cereals and pulses, can vary by a factor or two, depending on variety and fertilizer usage (38). These results indirectly confirmed the relative accuracy of the FCD; however, food composition analysis (phase C in Fig. 1), at least for protein, remains a recommended step.

In this RUTF prototype, the subjective texture criteria (not too gritty, not too fluid) and the criteria for a sufficiently high PDCAAS were met. If the PDCAAS had not been close to the desired value, the limiting essential amino acid in the formulation, lysine in our case, could have been included as a constraint (Table 1). Introducing a minimum constraint for the final content of lysine would have forced the model to include a greater proportion of lysine-rich foods in the formulation.

Taste constraints were also introduced in line with other LP studies in human nutrition (21). Trials confirmed that the RUTF prototype adequately met the sweetness preferences of both adults and children. However, it was found that it was not possible to meet the initial energy constraint. A global optimum model was successfully found by gradually relaxing the total energy constraint.

TABLE 3 Sensitivity analysis of the final optimized model[1]

	Constraint	Allowable increase	Allowable decrease
Nutritional			
Total energy, *kJ*	>2169	0.03	1.24
	<2299	<0.001	31.0
Protein energy/total energy	>0.10	0.004	1.18
	<0.12	<0.001	10.38
Fat energy/total energy	>0.45	77.85	<0.001
	<0.60	0.33	0.01
(n-3) Fatty acid energy/total energy	>0.003	2.87	<0.001
	>0.025	<0.001	8.54
(n-6) Fatty acid energy/total energy	>0.03	36.3	<0.001
	<0.10	<0.001	0.003
Palatability			
Sugar, *g*	>15	0.50	<0.001
	<18	<0.001	2.4
Sorghum, *g*	>7	0.02	0.87
	<10	3.0	<0.001
Texture			
Fat, *g*	>28	6.6	<0.001
	<36	<0.001	1.4
Maximum food ingredient weight			
Final amount, *g*	97	0.05	0.001

[1] All the values refer to 100 g of product. Calculations were performed using Microsoft Excel (2007) with the Solver add-in function and the Sensitivity Analysis Report option.

Goal programming, an alternative to LP, can also be applied to dietary problems and is described elsewhere (39). It allows the solution to have a range of OF rather than a single one (27). However, goal programming is more complex to apply. Because a solution could be found to the LP model by manually relaxing the energy constraint by only 0.2%, we avoided using this more laborious method.

In the present study, adjustments to the formulation (phase C in Fig. 1) were not needed. However, in another context, a sensitivity analysis could been used to guide the analyst on how much individual DV coefficients or constraints could be varied without requiring a change in the values of the DV or other constraints.

Our findings support the use of LP as a valuable tool to ensure that products meet nutritional design requirements while minimizing the cost of manufacture. According to UNICEF (40), 68% of Plumpy'nut's final overall price, excluding manufacturing and transport costs, consists of food ingredients. In Kenya in March 2008, 1 kg of Plumpy'nut cost ~$5.00 (personal communication, Malik Allouna, MSF/France, Kenya mission). This suggests that the indicative price for the Plumpy'nut food ingredients component was $3.40/kg. Therefore, the ingredient costs for the LP-derived RUTF prototype formulation (~$0.70/kg) is likely to be substantially cheaper, even after the addition of the micronutrient premix. Importantly, the lower transport and importation costs are also likely to result in a price advantage for locally produced RUTF. The regional agriculture economy may also benefit due to local purchase of the ingredients. However, more robust methods for economic assessment of RUF formulations are needed to support decision makers.

Future standard protocols for RUF design should address these economic aspects, including validated methods to obtain food price data in low-income countries for use in the LP model. In our study, it was challenging to find price data for ingredients that reliably represented seasonal fluctuations at national or regional levels. Briend et al. (25) estimated the economic impact and efficacy of novel nutrient-dense formulations against other current products, but such analysis goes beyond the goal of our current study.

Some constraints were highlighted in applying LP to design food formulations of this kind. The accuracy of the novel RUF was highly dependent on the quality of the available FCD. Since the 1970s, researchers have realized that most foods exhibit variations in composition and that a single table value cannot fully represent any particular food (38). Nutrient figures must therefore be considered as estimates (38). Improvements in FCD data collection and management have been proposed. For example, the INFOODS (33) and Codex Alimentarius Web pages (41) report information on standardized nutrient analyses, and recent international protocols and software (42) try to harmonize food names. Despite these initiatives, no FCD source, used for this LP exercise, reported coefficients of variation or SD figures despite their use being internationally recommended (38). Within WFDAS, the same item descriptors were sometimes reported more than once or did not specify the variety (e.g., in case of sorghum, white or red varieties), emphasizing the importance of the database item code for avoiding data selection errors.

In our study, lysine and tryptophan in soybean data from an American database (36) were higher than in merged non-American databases (35). This might have overestimated the final RUTF protein quality. However, the Kenyan manufacturer reported that U.S. soybeans were often present on the local market and so may be used in products manufactured in East Africa.

The oil descriptor used, palm oil, was different from the actual commodity used, which was palm olein oil. Palm olein is an industrially prepared fraction of palm oil. Therefore, it can be speculated that its nutrient composition, mainly in terms of (n-3) and (n-6) fatty acids, are different. Unfortunately, the laboratory used in this study, and probably most industrial laboratories in Africa, was not equipped to confirm the (n-3) and (n-6) fatty acid LP estimates. Rancidity of these nutrients is a major risk for the stability of food products with a high fat content. Therefore, close monitoring of its shelf life is important. At the time of writing this paper, the results from the RUTF shelf life study were not yet available.

In conclusion, this paper describes a widely applicable method for the rational design of therapeutic food products at minimum cost. The study provided a prototype formulation, which met all the predefined requirements, except for one relaxed by 0.2%, and also suggested, as a lesson learnt, the need for improved methods to determine the ingredient prices to use in the model. The RUTF cost (based only on food ingredients) was approximately 4- to 5-fold cheaper than the current standard product (food ingredients and premix). Using the methods described here, public health nutritionists and food technologists could apply these steps to design other RUF formulations, such as ready-to-use supplementary or complementary foods. However, the macronutrient contents of LP prototypes always need to be confirmed by food composition analysis and the finalized products trialed under field conditions before they can be recommended for general use (39,43).

Acknowledgments

F.D. conceptualized the study, compiled the food composition and price database and the RUTF nutritional and technological requirements, ran the LP, and wrote the draft manuscript; E.H.I.D. contributed to the discussion on the LP method; S.C. provided overall support to the research programme as a whole; and A.S. provided research supervision and contributed to revisions of this manuscript, whose final version all authors read and approved. We thank Insta Products EPZ Ltd, which manufactured the RUTF product for the laboratory analysis.

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Applied nutritional investigation

Development of a cross-over randomized trial method to determine the acceptability and safety of novel ready-to-use therapeutic foods

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ABSTRACT

Objective: To develop a method for determining the acceptability and safety of ready-to-use therapeutic foods (RUTF) before clinical trialing. Acceptability was defined using a combination of three consumption, nine safety, and six preference criteria. These were used to compare a soy/maize/sorghum RUTF (SMS-RUTFh), designed for the rehabilitation of human immunodeficiency virus/tuberculosis (HIV/TB) wasted adults, with a peanut-butter/milk-powder paste (P-RUTF; brand: Plumpy'nut) designed for pediatric treatment.

Methods: A cross-over, randomized, controlled trial was conducted in Kenya. Ten days of repeated measures of product intake by 41 HIV/TB patients, >18 y old, body mass index (BMI) 18-24 $kg \cdot m^{-2}$, 250 g were offered daily under direct observation as a replacement lunch meal. Consumption, comorbidity, and preferences were recorded.

Results: The study arms had similar age, sex, marital status, initial BMI, and middle upper-arm circumference. No carryover effect or serious adverse events were found. SMS-RUTFh energy intake was not statistically different from the control, when adjusted for BMI on day 1, and the presence of throat sores. General preference, taste, and sweetness scores were higher for SMS-RUTFh compared to the control ($P < 0.05$). Most consumption, safety, and preference criteria for SMS-RUTFh were satisfied except for the average number of days of nausea (0.16 versus 0.09 d) and vomiting (0.04 versus 0.02 d), which occurred with a higher frequency ($P < 0.05$).

Conclusion: SMS-RUTFh appears to be acceptable and can be safely clinically trialed, if close monitoring of vomiting and nausea is included. The method reported here is a useful and feasible approach for testing the acceptability of ready-to-use foods in low income countries.

Introduction

Ready-to-use therapeutic foods (RUTF) are high-energy, nutrient-dense products in which the powdered ingredients are usually suspended in fat. They do not require any preparation or the addition of water before ingestion [1] and can be stored for long periods without refrigeration. They can be individually packaged and can therefore be used effectively in situations with non-optimal hygiene conditions [1]. RUTFs are popular in feeding programs [2], including human immunodeficiency virus/tuberculosis (HIV/TB) interventions [1,3], because their use has been associated with an increase in successful treatment rates for severe acute malnutrition (SAM) when compared to other conventional treatments [4]. However, at present, the high price of RUTFs and their low regional availability hampers widespread use [5].

RUTF were initially developed for pediatric nutritional rehabilitation and the United Nations currently recommends [2,6] their use, at the community level, to help eradicate the one million child deaths that occur every year due to SAM [6]. In the next few years, $US2.6 billion will be spent on SAM treatment [4,7], and therefore, novel, cheaper, culturally acceptable, efficacious, and regionally manufactured products are already in

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demand for this patient group [2]. RUTF have also been used in feeding programs for HIV and TB patients and evidence from low-resource settings [8–14] shows that HIV/TB wasting in adults is still a public health issue in Sub-Saharan Africa, despite the increasing access to antiretroviral therapy.

In such countries, HIV programs aiming for nutritional rehabilitation and/or nutrition support tend to use a few specific types of food [10], usually either fortified blended foods [15] or RUTFs [16]. The most common commercial brand of RUTF is Plumpy'nut [17], which was designed for pediatric use and is the only one that has been clinically tested in several different studies [3,18–22]. In wasted adults, a number of factors have been shown to reduce compliance with Plumpy'nut including the taste of this pediatric formulation [23]. Moreover, the micronutrient densities in Plumpy'nut might not be appropriate for the needs of wasted adults with HIV/TB. For these reasons, there is demand for the development of a novel RUTF for this patient group.

Changes to the formulation of RUTF should be based on clinical evidence derived from randomized controlled trials (RCT) [24] but these are costly to implement. Therefore, robust data on product acceptability are required before implementation of a RCT, and determining adequate consumption, safety, and preference is a crucial early step in successful product development. However, at present there is no internationally endorsed protocol to assess the acceptability of products of this kind.

Here, we present a method for testing the acceptability of novel RUTF. To our knowledge, this is the first trial in a developing country that tests the acceptability of this type of product in wasted adults. The results of this randomized control study are presented according to recommended guidelines for cross-over trials [25].

Materials and methods

Trial and control products

The control product (Plumpy'nut; Nutriset, Malaunay, France [17]) contains peanut butter, milk powder, and a premix of vitamins and minerals and is referred to here as P-RUTF. The trial RUTF (Valid Nutrition, Derry Duff, Ireland, at Insta Ltd., Nairobi, Kenya) contained soybeans, maize, and sorghum, no micronutrients premix, and is referred to here as SMS-RUTFh ("h" standing for adult HIV/TB). Both products contained sugar (28 and 15 100 g^{-1}, respectively, for P-RUTF and SMS-RUTFh) and their macronutrients (energy, protein, lipids) closely met the United Nations requirements for RUTF (Table 1). Both their consistencies were pastelike, but their tastes and colors were different. The detailed formulation and clinical efficacy of SMS-RUTFh will be reported in another article (in preparation).

Study population, recruitment, and setting

The study was carried out in two locations, 2 km from each other, in Homa Bay, Kenya. The participants, enrolled after written informed consent, were patients recruited from the District hospital, supported by the Ministry of Health (MoH) and Médecins Sans Frontières-France (MSF). The patients from the two study groups met each other only at enrollment (day 1), and/or incidentally in the routine medical hospital visits. The participants, HIV and/or TB infected, were considered eligible if receiving antiretroviral therapy and/or TB treatment; age $\geq$18 y; and BMI between 18 and 24 $kg \cdot m^{-2}$ (Table 2). The exclusion criteria consisted of previous enrollment in a nutritional therapeutic program; oral problems that prevented adequate swallowing (typical AIDS oral thrush was not an exclusion criteria); and any specific food intolerance (e.g., peanut allergy). Patients missing more than 3 d were considered defaulters.

Study design

The study design was a two-arm cross-over randomized control trial. At enrollment, the patients were given a number from 1 to 2, randomly generated using an Excel spreadsheet (RAND function), that corresponded to one of the trial groups. Each group received one of the two products during each phase (AB/BA sequence). Under direct observation, during 2 wk (10 working days), water ad libitum and 250 g of one of the two products were offered to the patients as a replacement of the midday meal, with the message "please, eat as much as you wish." An extra 50 g was available on request. A maximum of 2 h was allowed to consume the product, and no leftovers could be taken away. After 2 wk (phase 1), the study was interrupted for 7 d (washout period) and then resumed for two more weeks (phase 2).

The professional background of the research staff included nursing, nutrition, and counseling. No one worked for the MoH or MSF, and the staff worked in a different study group each day, interviewing randomly assigned patients (ratio of staff members and patients: 1:3). In-depth questionnaires and focus group guidelines were provided in both English and the local language (Dholuo), after being anonymously back-translated. The packaging concealed the product identification.

Study procedure and outcomes

To consider RUTFh acceptable and safe, it had to fulfill the following criteria and subcriteria for consumption, safety, and preference (Tables 3–5).

Criterion 1: Consumption

The consumption criterion consisted of three subcriteria. The subcriteria "average consumption" was satisfied if average SMS-RUTFh intake was more than 75% (187.5 g) of the offered amount within 1 h (criterion 1.1; Table 3), whereas SMS-RUTFh "daily consumption" was met if its intake was higher than 75% of the offered food for more than 75% of the days on the trial (criterion 1.2). Finally, the "comparative energy intake" criterion (1.3) was satisfied if the average energy intake per kilogram of body weight was significantly higher than 75% of the energy intake from the P-RUTF.

Table 1
Comparison of macronutrients in the two RUTFs

	SMS-RUTFh		P-RUTF	References
Ingredients:	Soy beans, maize, sorghum, sugar, and oil		Peanut butter, milk powder, sugar and oil, vitamin and mineral premix	n.a.
Source:	International food composition databases	Laboratory results	Diop et al.(2003)	UN reference for pediatric RUTF (2007)
Reference number	[36,37]		[19]	[6]
Energy, $kJ \cdot kg^{-1}$	20 900	22 350	22 810	21 740-22 990
Protein, $g \cdot kg^{-1}$	120	153	136	n.a.
Protein/energy ratio, %	10	11	n.a.	10-12
Lipid, $g \cdot kg^{-1}$	310	336	357	n.a.
Lipid/Energy ratio, %	56	56	n.a.	45-60
(ω-6) Fatty acids/energy ratio, %	9	n.a.	n.a.	3-10
(ω-3) Fatty acids/energy ratio, %	0.8	n.a.	n.a.	0.3-2.5
Protein digestibility-corrected amino-acid score, %	82	n.a.	n.a.	n.a.

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Table 2
Characteristics of the participants at the start of the study (day 1), unless specified otherwise

	Group	
	1 ($n = 20$)	2 ($n = 21$)
Females, n (%)	17 (85.0)	15 (71.4)
Age,* y	34 (29; 42)	30 (27; 35)
Marital status, *n* (%)		
Currently married	10 (50.0)	12 (57.1)
Never been married	1 (5.0)	3 (14.3)
Previously married and now widower	9 (45.0)	6 (28.6)
BMI at enrollment,* $kg \cdot m^{-2}$	20.3 (18.9; 22.1)	19.9 (19.1; 21.8)
MUAC at enrollment,* mm	260 (229; 274)	266 (248; 280)
Diet Diversity Score†	7.5 (6.9; 8.2)	7.3 (6.7; 7.9)
Participants who had tasted P-RUTF at least once before the trial, n (%)	20 (100)	21 (100)

* Median and inter-quartile range (IQR).
† Medians and IQR of four measures over 2 wk, two consecutive days per week (phase 2 of the trial).

Criterion 2: Safety

SMS-RUTFh was considered acceptable from the safety point of view if participants did not report any of five comorbidity events more frequently than in the control product (criteria 2.1-2.5; Table 4). This parameter was expressed as the mean number of days in which morbidity events occurred during product consumption (10 d or less). Before the acceptability trial, microbiologic testing of SMS-RUTFh was performed. The results were in conformity with the United Nations specifications for such products [6].

Criterion 3: Preference

A product was considered preferred if its score was higher than the alternative in the following aspects: general preference, color, taste, sweetness, and texture (criteria 3.1-3.5; Table 5). At the end of the trial, each participant was asked to select the most preferred product (criterion 3.6), and two focus groups were held to investigate participants' experiences and perceptions that other methods may not have captured.

Data collection

Quantitative data were collected daily and included body weight, height, and middle upper-arm circumference (MUAC), weight of RUTF intake (Salter scale M021, max 500 ± 5 g), 24-h recall of nine clinical events, and individual eating duration. Body weight, MUAC, and height were collected daily, weekly, and at baseline, respectively. Individual interviews of all participants used a five-point Likert scale (with lower scores representing greater liking of a RUTF) [26], held to evaluate the preference for each product. Focus groups (30 to 40 min long) used preselected lists of discussion themes and the facilitators followed a written manual. Discussions undertaken in the local language were digitally recorded and transcribed into English, and twice a week, a diet diversity score (DDS) questionnaire (0-12 items type [27]) recorded the foods consumed at home.

Management of adverse events

Patients reporting any of the five clinical events for more than three consecutive days would have been immediately referred to the local clinic and withdrawn from the study if the cause was considered to be related to RUTF intake.

Sample size

A pediatric acceptability cross-over trial on RUTF [28] involved a sample size of 31 children, during 2 d of RUTF feeding, to detect a significant difference with α and β errors of 0.05 and 0.95. Its power calculation, based on of RUTF daily intake, considered 1 SD an acceptable difference to be detected. However, because previous research on RUTF acceptability was not available in adults, the nature of our study was exploratory. For this reason, when compared to the Indian pediatric study, the sample size ($n = 50$ including dropouts) and the number of feeding days (10 repeated measures/RUTF/individual) were both increased, but limited by the available budget.

Statistical methods

Student's *t* test and regression models were used to test for differences between continuous data. The Wilcoxon rank-sum (Mann-Whitney) test and sign test were used for non-normally distributed, unpaired, continuous data, whereas the Wilcoxon matched-pairs signed-rank test was used for non-normally distributed, paired continuous data, including the Likert scale five-item score. The double-sided Fisher exact test was used to compare categorical data, and odds ratios and confidence intervals were calculated. A linear regression model compared the energy intake of the two products after adjusting for potential confounders, including clinical events, socioeconomic data, and anthropometry at enrollment. Logistic regression models explored if the preference for a product could be influenced by group membership. Analysis of ordinal score for preference criteria was based on logistic (not ordinal) regression, after regrouping the data into two categories (scores 1 and score 2, 3, 4, or 5 of 5). This was because of the instability of the model, due to too few cases when cross-tabulating outcomes and predictors. When applicable, regression models benefitted from the robust standard error approach [29], so that the participant's series of repeated measurements were considered as individual clusters. Absence of a carryover effect was checked before treatment-effect analysis, following a method described elsewhere [30]. Statistical comparisons were two-tailed, and all testing was conducted at $\alpha = 0.05$, on per protocol data. EpiData version 3.1 software (Copenhagen, Denmark) was used for data entry and data analysis was undertaken using Stata IC v.10.

Ethical issues

This acceptability and safety trial was embedded into a larger research program that had ethical approval granted by the Kenyan Medical Research Institute and National Ethical Review Committee (SSC No. 1414) to test the clinical effectiveness of SMS-RUTFh.

Results

Characteristics of the participants

On June 30, 2008, the study staff enrolled 51 patients (Fig. 1) into a 5-wk trial. Two patients were excluded because they lived too far. Twenty-four and 25 participants were randomly allocated into groups 1 and 2, respectively. During the first phase of the trial, eight patients defaulted for more than 3 d and were excluded. Two of them stopped coming after the second day of the trial for unknown reasons and could not be traced. Six

Table 3
Product consumption in the two combined groups ($n_1 = 20$; $n_2 = 21$)

	RUTF consumption*			*P* Value†	*P* Value‡
	SMS-RUTFh ($n = 381$)	P-RUTF ($n = 398$)	Threshold		
	A	B			
Average consumption, $g \cdot d^{-1}$ (95%CI)	232.5 (218.9; 246.1)	243.0 (230.9; 255.0)	187.5§	<0.001	<0.001
Daily consumption,‖ % (95%CI)	86.1 (78.8; 93.4)	87.7 (81.4; 94.0)	75.0	<0.001	<0.001
Comparative energy intake kJ intake·kg body $wt^{-1} \cdot d^{-1}$ (95%CI)	94.9 (81.5; 108.3)	102.4 (96.0; 108.7)	76.8 (72.0; 81.4)¶	<0.001	<0.001

* Least-square means and 95% confidence intervals.
† *P* value between SMS-RUTFh and threshold.
‡ *P* value between P-RUTF and threshold.
§ The threshold is 0.75 times the 250 g initially provided.
‖ Percentage of days with consumption higher than 75% of the provided amount (250 g).
¶ The thresholds are 0.75 times the P-RUTF figures.

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Table 4
Safety criteria using 24-h morbidity recall in combined groups ($n_1 = 20$; $n_2 = 21$)

Criteria	Number of days* during which morbidity events occurred		P value
	SMS-RUTFh ($n = 381$)	P-RUTF ($n = 398$)	
	A	B	
C2.1: Nausea	0.16 (0.05; 0.47)	0.09 (0.05; 0.14)	0.04
C2.2: Vomiting	0.04 (0.01; 0.19)	0.02 (0.01; 0.04)	0.03
C2.3: Stomach pain	0.14 (0.05; 0.38)	0.16 (0.10; 0.25)	NS
C2.4: Flatulence	0.13 (0.05; 0.36)	0.16 (0.09; 0.26)	NS
C2.5: Diarrhea	0.36 (0.03; 0.70)	0.31 (0.13; 0.49)	NS

NS, non-significant
* Least-square mean and 95% confidence interval.

patients dropped out because of reasons not associated with product intake (transfer, other commitments). Forty-one patients successfully completed the study.

At admission, gender, marital status, BMI, and MUAC (Table 2) in the two groups were statistically similar. The DDS did not highlight any statistical significant difference in terms of kinds of food intake at household level, between the two groups. No difference was detected between the 2 wk DDS, nor within the same week for the same patients (Table 6). No carryover regarding amount and daily energy intake was reported ($P > 0.05$).

Measurement of acceptability

Measurement of consumption

Both average and daily consumption measurements were above the threshold ($P < 0.001$; Table 3) for SMS-TUTFh, confirming that all the patients consumed more than 75% of SMS-RUTFh within an hour (criterion 1.1); that acceptable consumption occurred on more than 75% of the trial days (criterion 1.2); and that its energy intake was higher than 75% of the P-RUTF intake in the two groups combined ($P < 0.001$) (criterion 1.3).

A linear regression model (robust standard error, 40-cluster analysis; $R^2 = 0.11$; $P = 0.01$; $N = 779$) showed that the difference between the energy intakes of the two products (SMS-RUTFh and P-RUTF) was not statistically significant ($P = 0.06$) when adjusted for confounders identified by a stepwise analysis (initial BMI, negatively correlated with energy intake, $P = 0.002$; presence of throat sores, negatively correlated, $P = 0.13$). Other potential confounders, which showed no or very small influence in the explored model and were not included, were age, and days of diarrhea, nausea, and flatulence. However, the statistical power of the available sample size was likely to be relatively small.

Table 5
Criteria for food preference (Likert score type*; five items) in the two groups ($n_1 = 20$; $n_2 = 21$), expressed on the last days of phase 1 and 2 of the trial

Criteria	SMS-RUTFh ($n = 39$)	P-RUTF ($n = 41$)	P value
C3.1: General preference			
Median (IQR)	1 (1; 2)	2 (2; 3)	<0.001
Mean (95%CI)	1.4 (1.2; 1.5)	2.4 (2.1; 2.8)	
C3.2: Color			
Median (IQR)	2 (1; 3)	2 (1; 3)	NS
Mean (95%CI)	2.0 (1.6; 2.4)	2.1 (1.7; 2.4)	
C3.3: Taste			
Median (IQR)	1 (1; 2)	3 (2; 4)	<0.001
Mean (95%CI)	1.5 (1.3; 1.8)	2.7 (2.3; 3.1)	
C3.4: Sweetness			
Median (IQR)	1 (1; 2)	3 (2; 4)	<0.001
Mean (95%CI)	1.7 (1.3; 2.0)	2.3 (2.5; 3.3)	
C3.5: Texture			
Median (IQR)	2 (1; 4)	2 (1; 2)	0.02
Mean (95%CI)	2.3 (1.8; 2.7)	1.7 (1.4; 1.9)	

NS, non-significant
* The scores range from 1 (very good) to 5 (very bad).

Evaluation of possible morbidity effects

Most types of morbidity did not differ according to product consumption (Table 4). Also, the average number of days with reported nausea and vomiting in participants consuming SMS-RUTFh was low (0.16 and 0.04 d of illness; 381 repeated daily measures). However, when applying robust standard error analysis, the data showed that these morbidities were significantly more frequent than when subjects were consuming P-RUTF (0.09 and 0.02; 398 repeated measures; $P = 0.04$ and 0.03). Nausea or vomiting never occurred for more than three consecutive days.

Measurement of patient's preference

Results from the fortnight interviews indicated higher scores for *general preference*, *taste*, and *sweetness* for SMS-RUTFh (criterion 3.1, 3.3, and 3.4; $P < 0.001$; Table 5), whereas no product was preferred in terms of color (criterion 3.2). SMS-RUTFh texture was less preferred than the control (criterion 3.5; $P = 0.02$).

On the last day of the trial, the whole sample ($n = 41$) failed to identify a final preference (criterion 3.6) for a specific product ($P = 0.8$). SMS-RUTFh and P-RUTF were preferred, respectively, by 52% (95%CI: 36; 69) and 48% (32; 64) of the participants. However for most patients, the preferred product was the one allocated to them in the first phase of the trial. For participants starting phase 1 with product A, the odds to prefer product A were 5.4 times (95% CI, 1.4-20.4) higher than for participants starting product A in phase 2 ($P = 0.02$).

The two focus groups organized on the last day supported the findings from the quantitative data and also suggested that "SMS-RUTFh texture needed to be refined," whereas "P-RUTF tasted salty" and "provoked more cases of flatulence." Moreover the patients were "not happy about changing the product from phase 1 to 2, once they had got accustomed to the first provided product" and felt that "the products were increasing weight" and physical "strength," "reducing hunger feelings." No morbidity event was mentioned during the focus groups.

Discussion

The present study demonstrated that most prestated criteria for acceptability of a novel RUF were satisfied, confirmed the utility of the proposed method and, at the same time, illustrated lessons that will contribute to improving future trials of a similar kind.

The acceptability of SMS-RUTFh

The findings of this study suggest that, in this participant group, SMS-RUTFh intake was adequate, and it was preferred in some regard to the current standard product. The patients could consume most of the trial product provided throughout the study, exceeding the selected threshold for adequate energy intake based on the control RUTF. Despite the higher (8%) energy density of P-RUTF, the energy intakes of the two products were statistically similar when adjusted for possible confounders, but the study might be underpowered to highlight a difference. Among the identified confounders, it can be speculated that throat sores reduce the swallowing capacity of the patients. A qualitative study on the compliance of the use of P-RUTF achieved a similar conclusion [23]. In SAM patients, cases of swallowing difficulty need to be detected early by medical staff and

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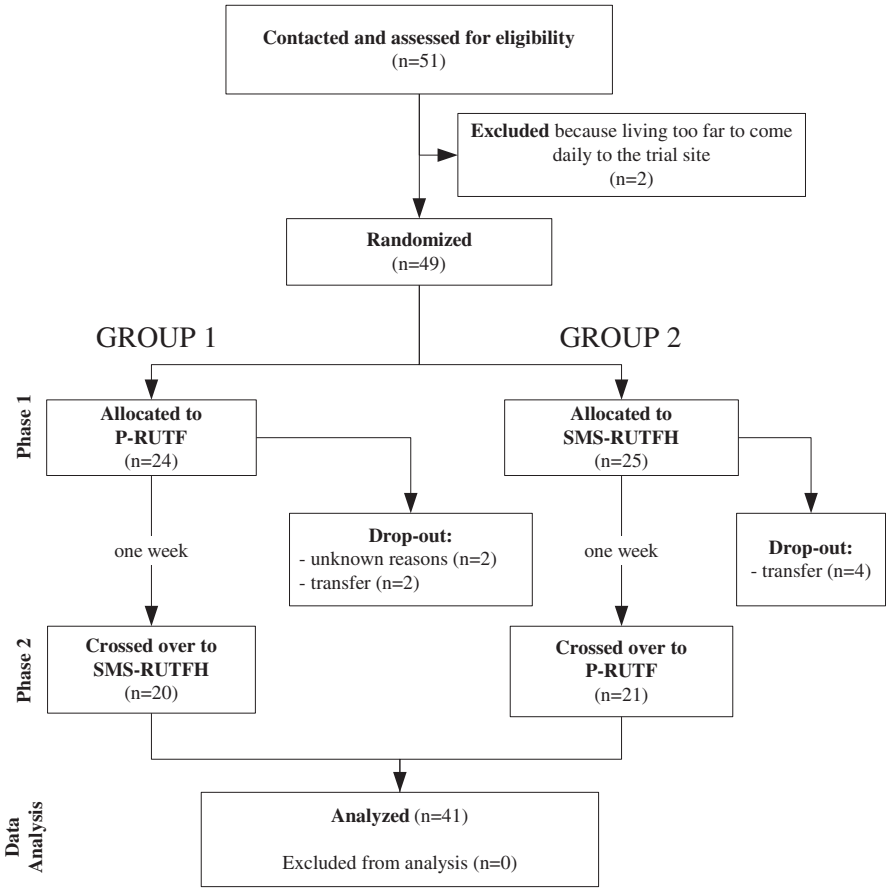

Fig. 1. Flow chart of the participants through the trial.

ideally addressed with appropriate in-patient care using therapeutic milk formulas (F75 and F100) [31]. As soon as the swallowing capacity is restored, generally in a few days, RUTF-based nutrition can be started and home-based care established.

The regression analysis found no evidence of increased morbidity associated with SMS-RUTFh consumption for most parameters. Although the frequencies of nausea and vomiting were higher in SMS-RUTFh than in the control product, they never affected participants for a prolonged period, and days of illness appeared to be scattered randomly along the time course of the trial. The regression models showed that the two comorbidities were not associated with a decreased energy intake. This suggests that the cause(s) might be due to chance or unknown factors, and that these and other events need close monitoring during the clinical trial.

The score for general preference was higher for SMS-RUTFh and its taste and sweetness were also preferred. However, its texture was less liked than P-RUTF, and this suggested the need for improved industrial processing to enhance the SMS-RUTFh consistency.

The order the RUTFs were offered to the participants was important. SMS-RUTFh consumption increased or decreased, according to whether it was provided as the first or second product. That might be because it was difficult for participants to adapt to a novel product once they are accustomed to the previous one.

Some constraints were highlighted. The participants of the trial were enrolled in the MoH/MSF HIV program and had all been exposed to P-RUTF. Information of this kind, acquired before direct experience, could have shaped the food consumption and preferences as suggested elsewhere [32].

Lesson learned about the method

This study highlighted important aspects in the application of methods to assess RUF acceptability. Among these, the results confirmed that a combination of both quantitative and qualitative measures is needed to capture the complex of factors influencing acceptability. The carryover effect analysis, recommended in cross-over studies [25], showed that the washout period (1 wk) was adequate and might be reduced for future trials.

The sample size ($n = 41$) compares favorably with an Indian study, whose sample size was powered for a difference of at least 1 SD. Determining the equivalence or non-inferiority of SMS-RUTFh to the current standard product, rather than its statistical superiority to prestated thresholds, represents an alternative study design used to validate robustly a novel therapy [33] but requires a large

Table 6
Diet diversity score* in phase 2 of the trial

Week	1		2	
	Tuesday	Thursday	Tuesday	Thursday
Group 1 ($n = 19$)	7.4 (6.5; 8.2)	7.7 (6.9; 8.5)	7.4 (6.5; 8.3)	7.6 (7.0; 8.2)
Group 2 ($n = 21$)	7.8 (7.1; 8.5)	6.7 (5.9; 7.6)	7.7 (6.8; 8.6)	6.9 (6.7; 7.7)
Groups combined	7.6 (7.1; 8.1)	7.2 (6.6; 7.8)	7.6 (6.9; 8.2)	7.2 (6.7; 7.7)

* Mean (95% confidence intervals).

sample size [34]. Other randomized trials [3,18,28], comparing RUTF with alternative food-based therapies, did not apply these methods. It is also important to note that the method described here is designed to be used in conducting an acceptability trial that precedes a RCT of clinical efficacy.

The study had some constraints. Ten days of RUTF intake, in each phase of our study, might have been too short to simulate the nutrition rehabilitation therapy in wasted adults (3 mo; MSF/Kenya, personal communication, 2008). The main use of RUTF is in outpatient and exclusive feeding programs. The study patients, instead, had access to the RUTF during only one daily meal, far from their households, while they were observed by the research staff.

For reasons explained elsewhere[35], the SMS-RUTF did not contain the micronutrients premix, which might alter the final taste of the product and the findings of the trial. A taste comparison between RUTF with and without premix therefore must be carried out to confirm these acceptability results.

Conclusion

Despite constraints, this exploratory study demonstrated the utility of this method and the acceptability of a novel, locally produced, RUTF. Its safety, mainly from the points of view of nausea and vomiting, should be monitored carefully. Lessons about the method were learned from the implementation of the study and should contribute to improving future trials.

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