Improving the treatment of Severe Acute Malnutrition in Childhood:

A randomized controlled trial of Synbiotic-enhanced therapeutic food with long term follow-up of post-treatment mortality and morbidity

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Thesis submitted to University College London in part fulfilment of the degree of:

PhD

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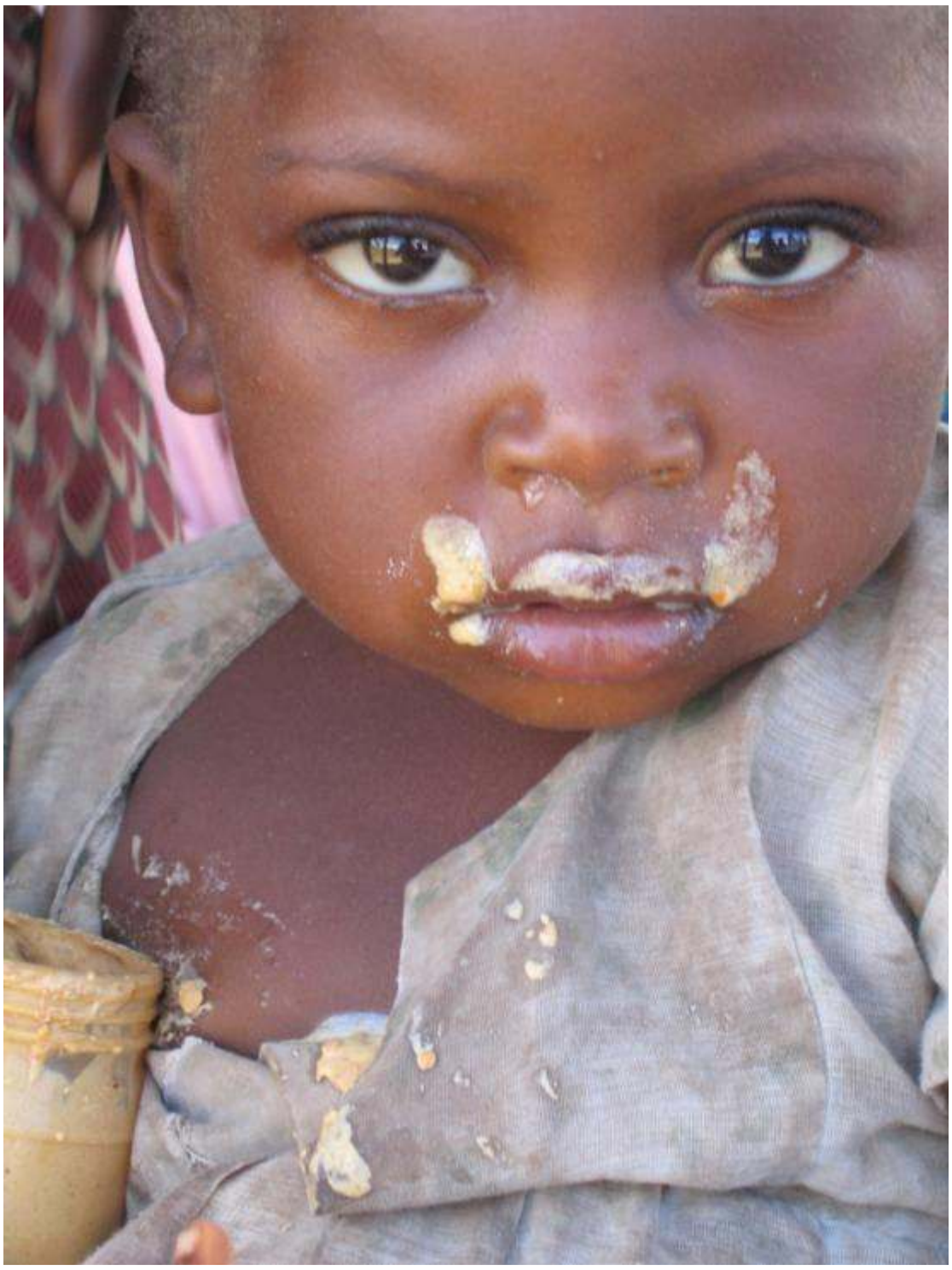

We are guilty of many errors and faults.
But our worst crime is abandoning the children,
neglecting the fountain of life.
Many of the things we need can wait.
The Child cannot.
Right now is the time his bones are being formed,
Right now his blood is being made,
Right now his senses are being developed.
To him we cannot answer "Tomorrow".
His name is *"TODAY"*

Gabriela Mistral
Nobel Prize-winning poet, Chile
(as quoted in "My Name is Today", David Morley & Hermione Lovell)

Food for Life

MOYO NUTRITION CENTRE
QECH, BLANTYRE

Declaration

I, Marko Kerac, 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.

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Marko Kerac

Abstract

BACKGROUND

Tackling severe acute malnutrition (SAM) is a global public health priority. This thesis explores two major influences on treatment outcomes:

-Treatment efficacy

-Patient-related risk factors

OBJECTIVES

1. To explore whether a pre/probiotic mixture (Synbiotic2000 Forte™) improves treatment outcomes (nutritional and clinical) in children affected by SAM.

2. To describe long term outcomes from SAM and identify key mortality risk factors.

METHODS

All 1024 malnourished children admitted to a therapeutic feeding centre in Malawi from July 2006 to March 2007 were eligible for:

The **PRONUT study** (Pre and **PRO**biotics in the treatment of severe acute mal**NUT**rition): 795 were recruited into a randomised, double-blind, placebo-controlled trial. They received Ready-to-Use Therapeutic Food either with or without Synbiotic2000 Forte™. Primary outcome was nutritional cure (weight-for-height >80% of NCHS median).

The **FUSAM study** (Long term **F**ollow-**U**p after **S**evere **A**cute **M**alnutrition): all children known to be still alive were followed up ≥1 year post discharge.

RESULTS

In **PRONUT**, nutritional cure was similar in both groups: 54%(215/399) for Synbiotic-enhanced RUTF and 51%(203/396) for controls (p=0.40). Main secondary outcomes were also similar (p>0.05).

Overall mortality from SAM was 41%(427/1024). Mortality was highest during initial inpatient treatment: 23%(238/1024). In **FUSAM,** 8%(84/1024) more died within 90 days of admission and 10%(105/1024) during long term follow-up. Cox regression identified HIV, low weight-for-height, low mid-upper arm circumference and low weight-for-age as major risk factors for death (p<0.001).

CONCLUSIONS

In this high-mortality setting, Synbiotic2000 Forte™, did not improve clinical or nutritional outcomes from SAM. A more promising strategy to improve outcomes might be to tackle the major risk factors for SAM mortality: HIV and severity of malnutrition disease. It is likely that earlier treatment would be beneficial. This is a focus of current strategies for both HIV and malnutrition. Rollout of such programmes should be supported and their impact on SAM evaluated.

Abbreviations & acronyms

ARV	Antiretroviral drugs (for treating HIV infection)
BF	Breast feeding (or breast-fed)
BMS	Breast-milk substitute
CIHD	Centre for International Health & Development, UCL, London
CF	Complementary foods / feeding
CFR	Case fatality rate
CHW	Community Health Worker
CMAM	Community Management of Acute Malnutrition
CSB	Corn Soy Blend
CTC	Community-based Therapeutic Care (original term for CMAM)
DHS	Demographic and Health Survey
DSMB	Data safety and monitoring board
EBF	Exclusive breast-feeding (or exclusively breast-fed)
EBM	Expressed breast milk
ENN	Emergency Nutrition Network, Oxford
GAM	Global Acute Malnutrition (= SAM + MAM)
HA	Height-for-Age
HAM	Height-for-Age % of median
HAZ	Height-for-Age Z-score
HCW	Healthcare worker
HIV	Human Immunodeficiency Virus
Infant(s)U6m	Infant(s) aged under 6 months (=0 to 5.9months)
IQR	Inter-quartile range
ITT	Intention to treat
IYCF	Infant and Young child feeding
LAB	Lactic acid bacteria
LBW	Low Birth Weight
LNS	Lipid nutrient supplement
MAM	Moderate Acute Malnutrition
MDG	Millennium Development Goal(s)
MoH	Ministry of Health
MUAC	Mid-Upper Arm Circumference
NCHS	National Centre for Health Statistics (Growth references)
NGO	Non-Governmental Organization
NRU	Nutritional Rehabilitation Units
SAM	Severe Acute Malnutrition
SC	Stabilization Centre
SS	Supplementary Suckling
SFP	Supplementary Feeding Programme (for moderate acute malnutrition)
TFC	Therapeutic Feeding Centre
TFP	Therapeutic Feeding Programme (for severe acute malnutrition)
WA	Weight-for-age
WAM	Weight-for-age % of median
WAZ	Weight-for-age Z-score
WH	Weight-for-height
WHM	Weight-for-height % of median
WHZ	Weight-for-height Z-score
WHO	World Health Organization
WHO-GS	World Health Organization Child Growth Standards, 2006
UN	United Nations

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I also dedicate this thesis to:
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- Finally – but most importantly - my wife Hannah, and my children, Toma and Milena: for the many blessings they bring to my life, and for sustaining and motivating me always.

[a] Please also see foreword for details of role of PhD student

Foreword

Severe Acute Malnutrition (SAM) affects an estimated 19 million children worldwide[1]. It is responsible for over 1 million deaths each year[2]. The past decade has seen important advances in how SAM is treated[3]. Yet in many settings, notably those where HIV is prevalent, mortality remains unacceptably high[4]. The work presented in this thesis is a small contribution towards wider efforts to better understand and more effectively tackle SAM.

Thesis outline

In **Chapter 1** I present the background to this thesis, outlining definitions of, treatment approaches to, and challenges around severe acute malnutrition. I highlight therapeutic food as a key intervention within the SAM treatment package and argue that a long term perspective is important to evaluating the true success and public health impact of treatment.

In **Chapter 2** I present the research hypotheses, aims and objectives

In **Chapter 3** I describe the core methodology, focusing on the study setting and population: all children admitted to MOYO nutritional rehabilitation unit, Queen Elizabeth Central Hospital, Blantyre, Malawi.

In **Chapter 4** I describe the **PRONUT** study (Pre and **PRO**biotics in the treatment of severe acute mal**NUT**rition), a randomised, double-blind efficacy trial.

In **Chapter 5** I describe the **FUSAM** (**F**ollow-**u**p of **S**evere **A**cute **M**alnutrition) study, a longitudinal cohort study describing long term outcomes of all patients admitted to MOYO.

In **Chapter 6** I discuss key findings from the two studies and their implications for current and future nutrition treatment programmes

In **Chapter 7** I conclude with recommendations for policy and research

The **Appendices** contain study forms, questionnaires, expanded results tables and other materials which are not included in the main body of the thesis for reasons of space and flow. Also listed are publications and presentations arising directly from and closely related to the research described.

Role of the investigator

This thesis would not have been possible without the help and support of many individuals and organizations listed in the acknowledgements. My involvement in nutrition research began in September 2003 during a year working as a junior doctor in the Paediatric Department of the College of Medicine, Queen Elizabeth Central Hospital, Malawi. Following a Public Health for Developing Countries MSc at the London School of Hygiene & Tropical Medicine (2004-5), I returned to Malawi in January 2006. Again full time in-country and working as a clinician in the paediatric department, mainly on 'MOYO' nutrition ward, I was also principal investigator of PRONUT, the core study of my PhD. I was responsible for developing and implementing an earlier version of the PRONUT protocol. This involved managing a ward-based research team, developing detailed clinical protocols, data collection instruments and the study database. I also expanded the scope of the study beyond its originally perceived remit. When it became apparent that long term patient follow-up was important both to PRONUT and its several sub-studies, I was co-applicant for a UNICEF grant funding the FUSAM study. I was responsible for the PRONUT / FUSAM database and led the major data analysis described in this thesis. For the published version of PRONUT I was lead author, writing the first version of the paper, co-ordinating and editing inputs from co-authors and submitting the final version.

Chapter 1
Severe Acute Malnutrition – Background

1.1 Global epidemiology and impact of malnutrition

Child malnutrition is a major international public health problem with consequences for both individuals and societies. Of 555 million children aged 0 to 5 years living in developing countries[1]:

> 177 million (32.0%) are stunted *(=chronic malnutrition)*
>
> 19 million (3.5%) are severely wasted *(=severe acute malnutrition)*
>
> 112 million (20.2%) are underweight *(=mixed malnutrition)*

Box 1 Malnutrition burden of disease in developing countries.
Source: Lancet Nutrition Series, 2008

The importance of malnutrition highlighted by a role in 6 of 8 Millennium Development Goals (MDGs)[5],[6]:

- ***MDG 1 (Eradicate extreme poverty and halve hunger) and MDG 4 (Reduce child mortality)***

Malnutrition interacts with other major causes of mortality (***figure 1***) and underlies anywhere from 35%[1] to over 50% of all under-5 child deaths[7],[8]. Severe acute malnutrition (SAM), though the least prevalent form of malnutrition is associated with the high mortality risk. SAM alone causes some 1-2 million deaths per year.[9]

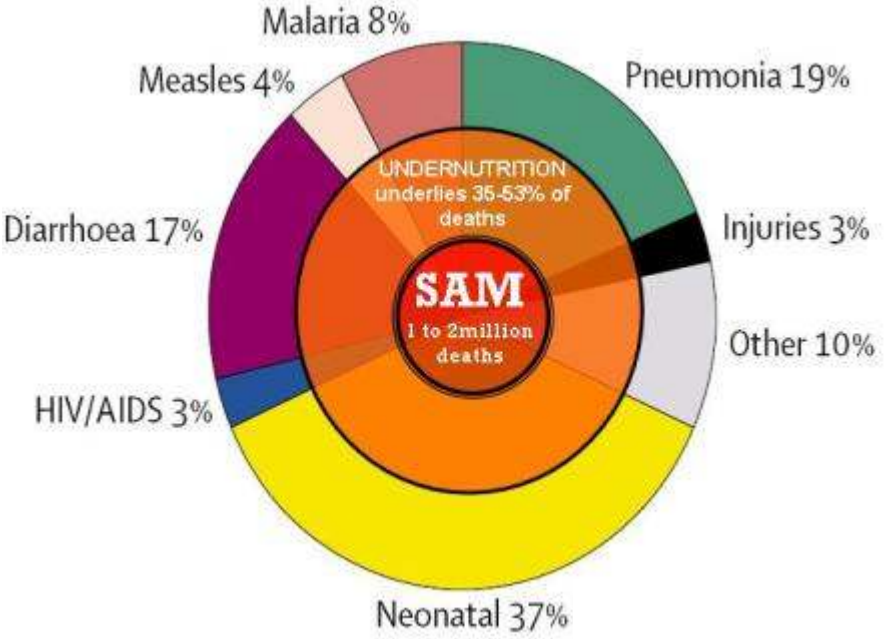


Figure 1 Causes of death in under-5 children worldwide
Modified from the Lancet 2005; 365: 1147–52

Malnutrition also has implications for:

- **MDG 2 - Universal primary education:** malnutrition impairs school performance[10];
- **MDG 3 - Gender equality:** malnourished girls are less likely to stay in school and receive the education so vital to their empowerment[11];
- **MDG 5 - Maternal Health:** malnourished girls not reaching their full adult physical potential are at increased risk of maternity-related problems[12];
- **MDG 6 - Combat HIV/AIDS, malaria & other diseases:** nutrition and infection interact: malnutrition can increase vulnerability to and severity of infection; infection can contribute to a worsening of malnutrition[13],[14]

The effects of malnutrition are not just short term and confined to the affected individual but may have important long term and intergenerational consequences (***figure 2***). Effectively tackling malnutrition is therefore a global health priority with potential for far reaching impact.

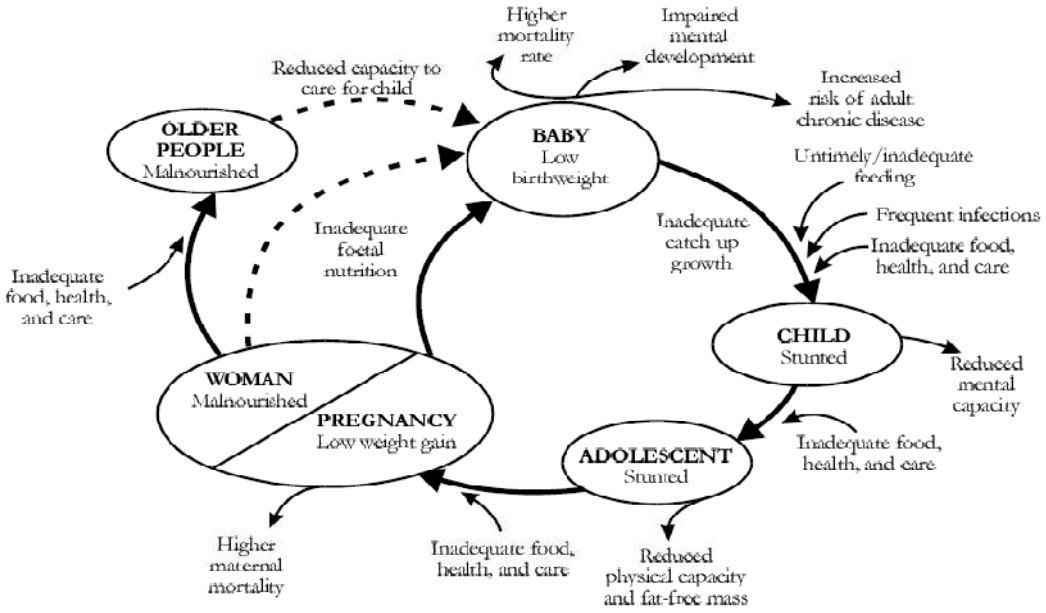


Figure 2 Life course and intergenerational effects of malnutrition

(source: World Nutrition Situation, 4th Report)

Whilst the various forms of malnutrition have different implications for different outcomes, they often overlap and can affect the same individual child. Specific micronutrient malnutrition may also be present. This thesis focuses on SAM because:

- it is associated with particularly high mortality risk

- it is the current admission criterion for therapeutic feeding programmes (***section 1.3***)

Other forms are also however acknowledged as important and will be explored, particularly when describing long term outcomes following an episode of SAM.

1.2 Case definitions of Severe Acute Malnutrition

Severe acute malnutrition (SAM) encompasses both wasting (loss of body mass) and oedematous malnutrition, commonly known as kwashiorkor. Reflecting changes in the way SAM is treated, details of the case definition have evolved over recent years:

1.2.1 'Classical' WHO definition

In the seminal 1999 guideline, "Management of severe malnutrition: a manual for physicians and other senior health workers"[15], the World Health Organization defined SAM as:

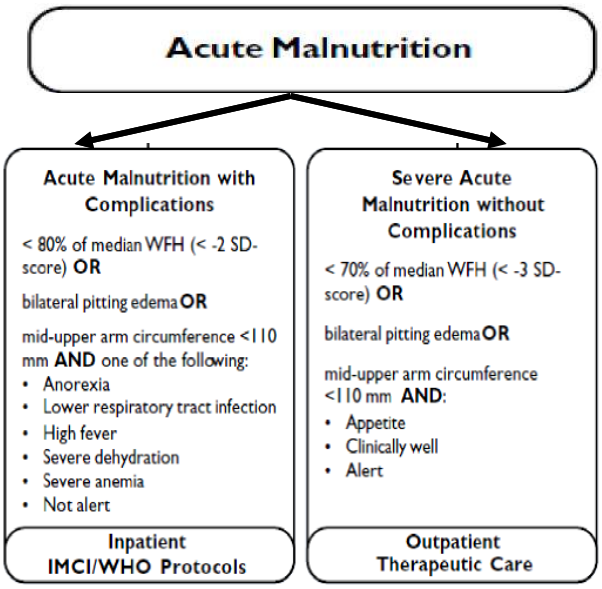
> Weight-for-height <-3 standard deviations (z-scores) from a reference median
>
> (WHZ<-3)
>
> *or*
>
> oedematous malnutrition

Box 2 World Health Organization (1999) definition of SAM

At the time, the median was based on National Centre for Health Statistics (NCHS) growth references. Weight-for height <70% of the median (<70% WHM) was also recognised as defining SAM. This is similar but not identical to WHZ <-3. Whilst the former was ideal for reporting population nutritional status, WHM became the commonest criterion for assessing individuals for possible entry to feeding and other treatment programmes[16].

1.2.2 'Modified' definition - complicated and uncomplicated SAM

In a 2003 letter to the Lancet, Collins & Yates[17] proposed an important modification to the WHO definition. The aim was to differentiate between children who could be safely treated as outpatients and those who needed more intensive inpatient care. Clinical features were considered alongside anthropometric status:



In this new classification, children with moderate acute malnutrition (70% to <80% WHM or -3 to -2 WHZ) and complications were also considered eligible for inpatient care.

Figure 3 Complicated and uncomplicated malnutrition

Source: Adapted from FANTA Technical note 8. Community-based Therapeutic Care. Grobler-Tanner & Collins, 2004[18]

1.2.3 Mid-upper Arm circumference

Mid-upper arm circumference (MUAC) reflects muscle and subcutaneous fat mass and is a useful marker of acute malnutrition. Evidence suggests strong associations between low MUAC and high mortality[19]. Whilst not noted in the WHO 1999 guidelines, many countries and organizations currently use MUAC <110mm as an independent criterion defining SAM in children aged 6 to <60 months[16]. A major advantage is simplicity and suitability for community health workers who are increasingly engaged in field-based case finding. With new WHO growth standards, the threshold has been changed from <110mm to <115mm[20] (see below).

1.2.4 World Health Organization Child Growth Standards[21]

In 2006, WHO released new 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"[22]. A May 2009 joint statement from WHO and UNCIEF endorsed the new standards for identifying SAM[20]. Whilst they are a considerable technical improvement on the old growth references[23], it is important to recognise key differences between NCHS and WHO-defined SAM, notably in terms of potential clinical caseload[16]:

Table 1 NCHS and WHO growth norms used to define SAM

	NCHS	***WHO***
KEY CHARACTERISITICS		
Type of growth curve	Reference	Standard
ACUTE MALNUTRITION CASE DEFINITIONS		
Oedematous malnutrition = SAM (irrespective of weight-for-height)	Yes	Yes
SAM (% of median)	<70% weight-for-height (WHM)	not used
SAM (z-score)	<-3z weight-for-height (WHZ)	<-3z weight-for-height (WHZ)
MUAC-defined SAM *(6 to <60m children)*	<110mm	<115mm
IMPLICATIONS FOR CLINICAL CASELOAD *relative numbers of 6 to <60 month children diagnosed with:*		
SAM, as defined by: *WHZ (NCHS) to WHZ (WHO)*	1 (reference)	Increase in numbers diagnosed (2 to 4x increase)[20]
SAM defined by: *WHM (NCHS) to WHZ (WHO)*	1 (reference)	Large increase in numbers diagnosed (8x increase in one study)[24]

1.2.5 *Case definition of SAM used in this thesis*

The fieldwork described in this thesis was done in Malawi from January 2006 to September 2008. At this time, Malawi national guidelines[25] defined SAM as:

> Weight-for-height <70% median (NCHS references)
> *or*
> kwashiorkor (oedematous malnutrition)
> *or*
> MUAC <11cm

Box 3 Case definition of SAM used in this thesis (following Malawi National Guidelines)

This definition is consistent with international best practice. Also consistent with international best practice, summary anthropometry in this thesis is expressed mainly as z-scores. As will be described in detail in chapter 3, National guidelines recognised complicated and uncomplicated SAM but the study setting at the time had no separate outpatient centres for direct treatment of uncomplicated disease. Children with uncomplicated SAM were thus admitted and treated together with children who had SAM plus complications.

1.2.6 *Why case definition matters*

The reason for reviewing case definitions is to emphasise that each will select a slightly different group of patients. Since nutritional status is a continuum, diagnosing a discrete category of SAM is inevitably challenging. Though anthropometry is key, it is not anthropometry that matters most. What matters is that it reflects other more important processes and risks, notably risk of death (see figure). Declining weight-for-height is related to[26] but not synonymous with[17] increasing risk of mortality. Implications of newer SAM definitions will be discussed in chapter 6. For now, it is important only to note that findings based on one group should only be generalised to another with caution.

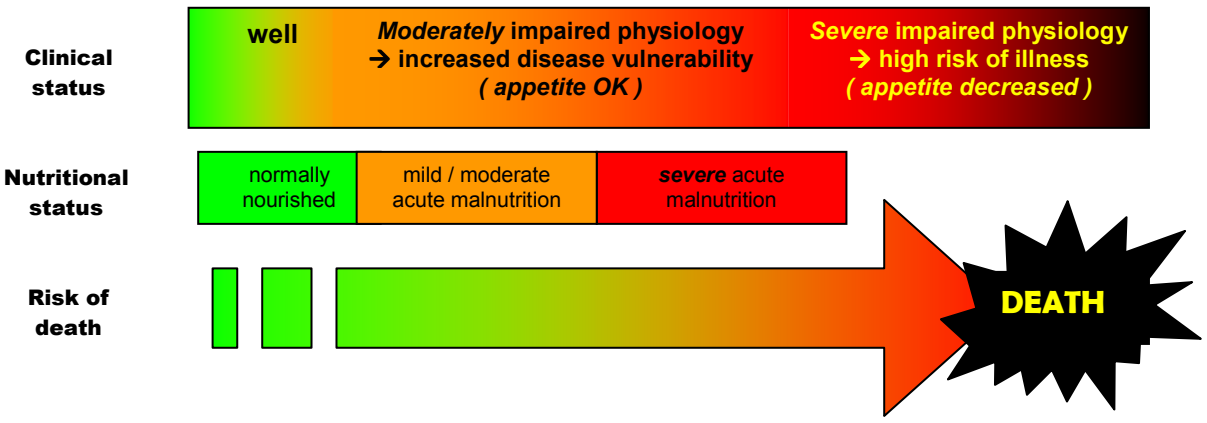


Figure 4 Conceptual illustration of continuous processes and discrete categories in 'malnutrition'

Shaded arrow indicates the progressive nature of the risks. The boxes indicate that for practical programme use, categories necessary.

1.3 Treatment programmes for childhood SAM

Approaches to SAM have evolved considerably over recent years, even over time spanning this PhD fieldwork. To contextualise the research results in this thesis and their potential application to different types of treatment programme, this section gives an overview of common strategies.

1.3.1 Conceptual frameworks and root causes

Ideal strategies for tackling SAM involve a range of approaches, with resources allocated in proportion to cost-effectiveness and impact. A public health perspective recognises that the problem can be tackled at three levels[27]:

- Primary prevention = reducing the development (incidence) of SAM
- Secondary prevention = reducing prevalence of SAM by earlier detection of or better treatment shortening the duration of an episode of malnutrition
- Tertiary prevention = reducing the negative impacts of established SAM

These can also be understood using the UNICEF conceptual framework below:

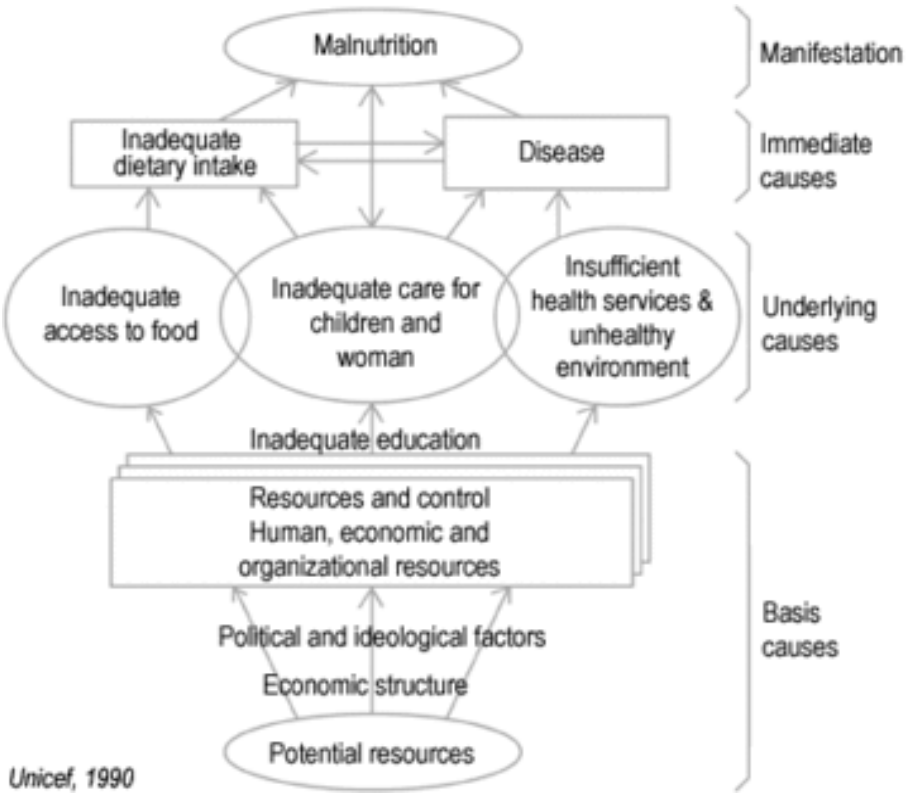


Figure 5 UNICEF conceptual framework for malnutrition

(Source: State of the World's Children 1998)

1.3.2 The Pathophysiology of SAM

Understanding the pathophysiology of SAM is key to optimising its treatment. Whilst some details remain to be elucidated (e.g. why kwashiorkor is more common in some populations than others; what is its exact cause[28]), many features are well understood and help shape and guide treatment strategies. The main features of SAM are outlined in detail in J.C.Waterlow's authoritative book "Protein-Energy Malnutrition"[29] and are summarized from that source below:

- "A child with SAM is not just a scaled-down version of a normal child and must be treated accordingly.
- When deprived of 'normal' nutrition over a period of time, the body often 'adapts', to the new state with changes in metabolism, structure and organ function.
- There is preferential loss of muscle, fat and probably of skin (tissues which in resting state have relatively low metabolic activity) whilst essential organs like the brain are relatively well preserved.
- Electrolyte and mineral balance is often disturbed. e.g. serum potassium levels are low; total body sodium is high but there is a paradoxical tendency to serum hyponatremia (a very poor prognostic sign); serum and urine phosphorous is low
- Anaemia is common (though different studies suggest different underlying causes)
- There are adverse effects on organ structure and function:
    - Cardiac impairment: with corresponding risk of cardiac failure
    - Liver impairment: notably if there are fatty infiltrations (fatty liver is often associated with kwashiorkor but is also found in marasmus)
    - Reduced pancreatic enzyme production
    - Impaired gut function: due to a multiplicity of causes ranging from a damaged epithelium to disturbed gut microflora and leading to several effects including reduced absorptive capacity and weakened immune barrier function
    - Impaired renal function: including a reduced ability to excrete acid and sodium and a reduced ability to concentrate urine
    - Skin changes: most notably the 'flaky paint dermatosis' of kwashiorkor
    - Impaired nervous system structure and function (though the brain is relatively protected from nutritional adversity, it is important to note that the protection is not absolute)
- There are important metabolic changes, including impaired capacity for heat production, with corresponding higher risk of hypothermia
- Endocrine changes include:

    - Those that reflect or determine short term issues e.g. impaired insulin function and impaired ability to manage blood sugars leading to risk of hypoglycaemia; increased glucocorticoid production
    - Those that influence long term growth e.g. thyroid hormone and somatomedin
- Trace elements are often depleted and can contribute to poor overall outcomes e.g. selenium, zinc and vanadium[30],[31]
- The immune system is impaired and contributes to greater vulnerability to infection; greater potential severity of infection; altered manifestations of infection (e.g. children with severe SAM may not be able to mount a febrile response as would be normal)."

Treatment strategies, notably those pioneered at the Tropical Metabolism Research Unit in Jamaica in the 1970's to 1990's recognised and took account of these pathophysiological features. Excellent outcomes were achieved by a multifaceted approach which directly addressed the core problems e.g.:

- Specially formulated feeds which take into account common micronutrient and electrolyte deficiencies as well as energy and protein needs
- A 'phased' approach to treatment whereby a physiologically vulnerable child is first 'stabilized' before moving onto a more nutrient-dense 'recovery phase' diet
- Careful rehydration to avoid fluid overload and potential death from heart failure
- Routine antibiotics in light of the high infection risk

This structured, pathophysiologically-informed approach was eventually taken up by the World Health Organization and became the basis of the "10 steps" treatment guideline described in the next section (see in particular ***table 2***).

The same pathophysiological understanding still underpins all current treatments for SAM. Since appetite is affected by and thus becomes a clinically useful proxy of the severity of pathophysiological compromise, it is one of the key clinical features used to assess children at admission to treatment. A poor or absent appetite reflects a vulnerable and sick child with complicated SAM (see ***figure 3***) in need of intensive inpatient treatment and close monitoring. In contrast, an active appetite reflects a child with uncomplicated SAM: he/she may have anthropometrically defined SAM but is clinically stable enough to be considered for home-based treatment.

1.3.3 Therapeutic & Supplementary Feeding Programmes (TFP & SFP)

Therapeutic Feeding Programmes (TFPs) are the mainstay of current SAM treatment. They focus on established SAM (tertiary prevention), though in-programme activities such as health education may have secondary and primary preventive effects on SAM recurrence in the same family or community. The aim of a TFP is to minimise mortality and morbidity by restoring normal nutritional status.

An important part of the TFP treatment package is a diet of therapeutic food. This is defined by a micro and macronutrient content specially formulated for SAM[9]. As indicated by the pathophysiology of SAM, other treatments such as antibiotics for infection are also essential and are provided as routine.

Supplementary Feeding Programmes (SFPs) are closely related to TFPs but focus on moderate acute malnutrition (MAM). Similar to TFPs, they aim to restore normal nutritional status through provision of supplementary foods such as corn-soy blend. Numbers of children affected by MAM are considerably greater than by SAM and SFPs are thus important in their own right. Individual mortality risk is however lower, so the general approach is outpatient based and less intensive. Relevant to this thesis, SFPs serve two key roles:

- In an ideal setting, SFPs would prevent severe wasting because they would enrol and treat children before their malnutrition becomes severe. (Pre-empting kwashiorkor would be more difficult given no clearly defined prodromal phase to predict which children will develop disease)
- Following successful therapeutic treatment of SAM, children are often referred to an SFP. In this role, SFPs monitor continued wellbeing and aim to prevent relapse. If such a SFP 'safety net' is not present, some TFPs keep children enrolled for longer or adjust their discharge criteria to a higher weight-for-height target.

1.3.4 Inpatient TFPs – Therapeutic Feeding Centres (Nutritional Rehabilitation Units)

Traditionally, children with SAM are treated in inpatient TFPs called therapeutic feeding centres (TFCs) or nutritional rehabilitation units (NRUs). Focus is on case management of the individual patient. WHO's 1999 guideline, "Management of severe malnutrition: a manual for physicians and other senior health workers" is a key resource describing the main features of TFC care[32]. It is based on the pathophysiological understandings described in ***section 1.3.2***. Phased treatment is central to the strategy. This recognises that children with SAM are vulnerable and often have very compromised physiological systems which need to recover slowly.

Picture 1 Inpatient TFC in Malawi (the setting of this PhD research)

Nutritional treatment in the 'stabilization phase' (also known as 'phase 1') uses 'F75' milk. 'Rehabilitation' or 'phase 2' progresses to more nutrient dense 'F100' milk feeds. Some protocols suggest an intermediary 'transition phase'.

F75 and F100 milks can either be:

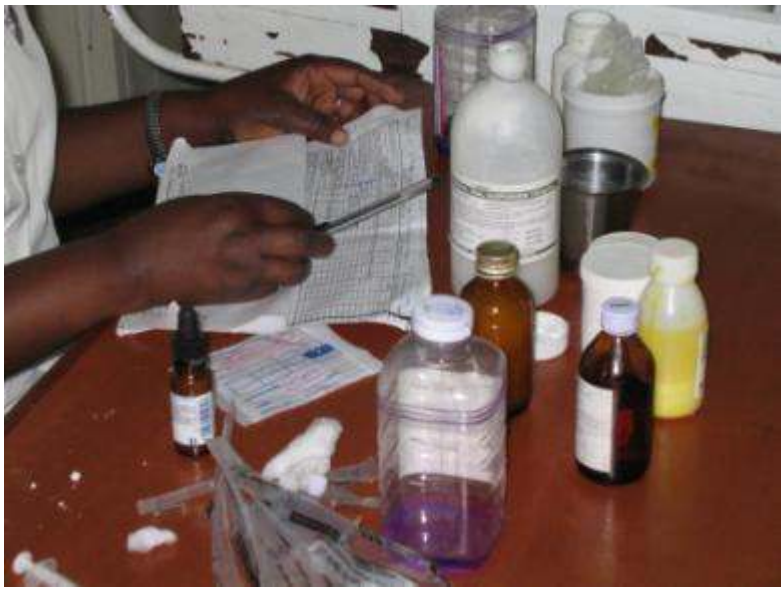
- locally made using commonly available ingredients fortified with a micronutrient mix
- imported as a dry powder 'formula' milk which needs reconstitution in heated water.

Picture 2 Distributing therapeutic milk

Medical treatments in WHO 1999 include routine antibiotics for infection.

Also recognised is the importance of environment and psychosocial interventions towards improving outcomes from SAM.

Nutritional, clinical and psychosocial treatments are all integrated in what is often known as the "10 steps approach" ***(table 2)***



Picture 3 Distributing medical treatments for SAM

Table 2 WHO '10 Step' treatment of SAM

(source - WHO 1999)[15]

Activity	Initial treatment:		Rehabilitation:	Follow-up:
	days 1–2	days 3–7	weeks 2–6	weeks 7–26
Treat or prevent: hypoglycaemia	→			
hypothermia	→			
dehydration	→			
Correct electrolyte imbalance	→	→	→	
Treat infection	→			
Correct micronutrient deficiencies	← without iron	→	← with iron →	
Begin feeding	→			
Increase feeding to recover lost weight ("catch-up growth")		→	→	→
Stimulate emotional and sensorial development	→	→	→	→
Prepare for discharge		→	→	

1.3.5 Community Management of Acute Malnutrition (CMAM)

CMAM (originally and still often known as CTC, Community-based Therapeutic Care[33]) is an integrated TFP strategy which combines with and complements WHO (1999) by focusing on population coverage[18],[34]. It aims to maximise public health impact by treating large numbers of SAM-affected children. The modified SAM classification is used to distinguish between:

- Sick children ('complicated' SAM) who need intensive inpatient care
- Clinically stable, well children ('uncomplicated' SAM) who can safely be treated at home

Though community-based approaches to SAM are not new[35], CTC was the first to formalize a detailed strategy and framework[36],[18] Key features of the treatment model are[34]:

- *Access & high coverage* - Large numbers of treatment centres ensure easy access and consequent high programme coverage.
- *Timeliness* - Active case finding aims to recognise and treat children *before* they develop complicated SAM. Most can thus be admitted to the 'Outpatient Treatment Programme' (OTP). The few with complicated SAM go via inpatient 'stabilization centres' (SCs). Once clinically improved/stable, they are transferred to the OTP to complete their treatment
- *Sectoral integration* - CTC aims to integrate with other programmes (such as supplementary feeding programmes) and address wider factors underlying malnutrition.
- *Capacity building* - CTC aims to empower and encourage local communities, and existing structures and networks.

The basic principles of CTC/CMAM have since been incorporated into numerous national SAM guidelines and in 2007 were endorsed by major UN agencies[9]. The structure of and 'flow' through a typical programme is illustrated:[37]

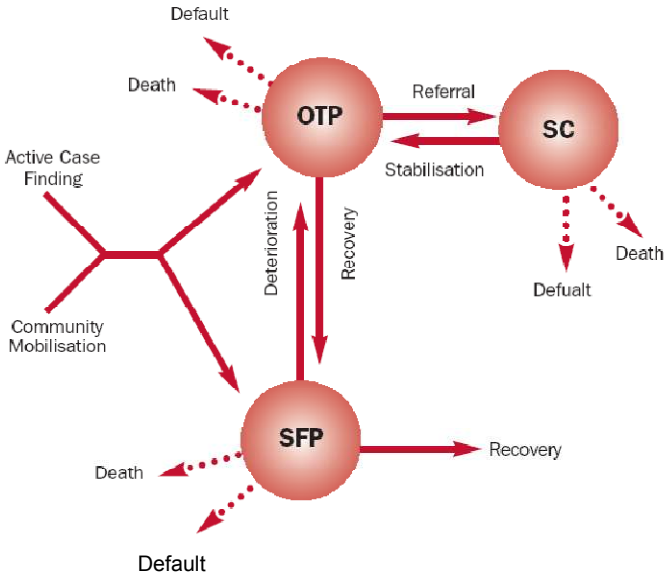


Figure 6 Structure of and patient 'flow' within a CMAM TFP

(source Valid CTC Manual, 2006)[37]

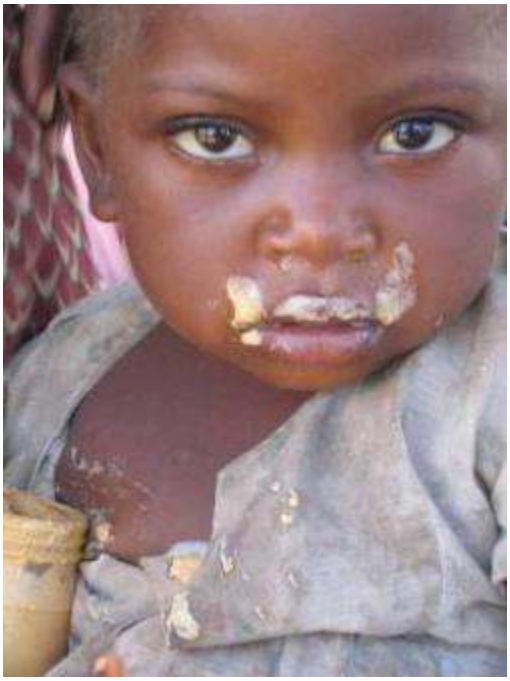
1.4 RUTF (Ready-to-Use Therapeutic Foods)

Efficacious therapeutic food is central to a successful TFP. Ready-to-Use Therapeutic Food (RUTF) is the generic term for a nutrient-dense solid or semi-solid food paste suitable for children with SAM. It is the key technology making CMAM possible.

1.4.1 History & Development of 'Standard', peanut-based RUTF

Non-milk diets for malnutrition have a long history[38]. In the 1970's for example, Red Cross emergency teams used milk biscuits. The emphasis, as today, was on a commodity providing high nutrient quality yet easy to transport, store, and eat without complex or time-consuming preparation.

The RUTF currently in use is based on the nutrient profile of F100 milk, the current 'gold standard' diet for SAM[15],[9]. (see table below). The commonest recipe comprises a peanut butter base (25% weight), full fat milk powder (30% weight), sugar (28% weight), vegetable oil (15% weight) and multivitamin/mineral mix (1.6%, including iron)[39]. One of the earliest trials comparing this RUTF to F100 was in 1999 in Chad. Higher energy intake was observed in the RUTF group[40]. Another study influencing subsequent practice was published in 2003. In Senegal, an open label randomised trial tested the RUTF against F100 milk. Weight gain and duration of nutritional rehabilitation were both significantly better in the RUTF group[41].



Picture 4 Eating RUTF

Nutritional composition	
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

Table 3 RUTF nutrient profile

Source: UNICEF/WHO/WFP joint statement, 2007

1.4.2 The potential role of alternative recipe RUTF

Peanut-based RUTF (also widely known under the largest manufacturer's trade name, Plumpy'nut) remains dominant in CMAM programmes worldwide. This reflects the rapid and recent evolution of CMAM. Much of the background research was conducted using the best known, best validated, formulation described in Chad[40] & Senegal[41]. As programmes have scaled up, so has the manufacturing capacity and demand for this same peanut RUTF. So however have questions about alternative recipes.

Three issues underlie discussions about alternative RUTF recipes:

i) Cost minimization

RUTF is the main cost component[42] of a CMAM feeding programme. Cheaper but equally effective recipes would improve cost-effectiveness.

ii) Local ownership & local benefits

Peanuts are not as common or acceptable in all parts of the world as in the African countries where the peanut RUTF recipe was first developed and tested. Alternative recipes based on staples such as rice, chickpea or soya have the potential to better support local needs and local markets[43],[44]. Using local ingredients to benefit local economies and make locally tailored RUTFs was one of the original principles underlying CMAM.

iii) Enhanced efficacy

Alternative recipes have the potential to improve on the efficacy of current ones. This is the rationale behind addition of a functional food to standard RUTF in this thesis.

1.4.3 A note on RUTF (Ready-to-Use Therapeutic Food) & LNS (Lipid Nutrient Supplement) terminology

Since this thesis was started, interest in "Ready to Use foods" has blossomed. With the growing evidence-base underlining RUTF for SAM, investigators and programme managers have been quick to try other plausible uses. These include for supplementary feeding, for HIV and for primary prevention of malnutrition. Lacking alternatives, the RUTF recipe originally described for SAM has been used for all these purposes. RUTF should however have a very precise use and meaning as a therapeutic food for SAM alone – this is how it is used in this thesis. Expanded uses do though need to be recognized. This is because functional additives, as explored in PRONUT may be relevant to conditions other than SAM.

"Ready-to-Use" food is a generic term, subsets of which include:

- RU**T**F = ready-to-use **THERAPEUTIC** food – for SAM
- RU**S**F = ready-to-use **SUPPLEMENTARY** food – for MAM
- RU**C**F = ready-to-use **COMPLEMENTARY** food – for general use as a complementary food or for preventing malnutrition
- RU_F-**H** = any of the above for **HIV**

Ideally these would all be tailored to the particular needs of their patient group. Such work is ongoing.

Lastly, lipid-nutrient supplement (LNS) nomenclature needs to be noted as its use is increasing. LNS are defined as multiple micronutrient supplements which have lipid as the primary source of energy[45]. RUTF described in this thesis is therefore a type of LNS.

1.5 Evidence gaps towards improved feeding programme impact

A 1996 review of SAM treatment outcomes reported case fatality rates averaging 20-30% and sometimes as high as 50-60%[46]. WHO 1999 guidelines were part of a successful international initiative addressing the problem[47],[48]. CMAM programmes have continued to build on this success and report data supporting both low mortality and high programme coverage[49]. Given this existing evidence base for SAM treatment, some have argued that rollout of existing technologies and interventions should now be the international health priority[50, 51]. In this thesis, I fully agree with that sentiment. I would add however that scaling-up what is known is not incompatible with exploring what is not known. Knowledge gaps with potential to improve public health impact remain and are the motivation behind the work described.

1.5.1 What is the true public health impact of a TFP?

Most TFPs report outcomes when children are discharged from their care, typically after 2-3 months treatment. Good outcomes at this stage are important but not necessarily sufficient. True public health impact depends on sustained, longer term benefit. Illustrating with an extreme hypothetical example:

- Programme A has a 5% short term, in-programme mortality. Yet if a further 50% of children die over the subsequent year, there is an obvious problem. This would not necessarily be identified through routine reporting. Many TFPs have neither the systems nor resources for long term follow-up.

- Programme B has a 30% in-programme mortality. Yet if only 5% of the survivors subsequently die, then the public health impact is actually greater than in A.

To date, few studies have explored long term outcomes following an episode of SAM. The FUSAM sub-project addresses this issue. Consistency with and differences from this limited body of existing research will be discussed in chapter 6.

1.5.2 Can poor outcomes in an HIV prevalent setting be improved?

HIV is well recognised as having a major impact on both presentation and outcomes from SAM[52]. A recent meta analysis shows mortality among HIV infected children with SAM to be consistently and significantly higher than in those without underlying HIV. (30.4 vs. 8.4%, RR = 2.81, 95% CI 2.04—3.87)[53]. Interventions with the potential to improve SAM outcomes in HIV prevalent settings are therefore important[4]: PRONUT describes the potential of functional food to fulfil this role.

Second, improving SAM outcomes in an HIV prevalent setting requires better understanding of factors, apart from the HIV itself, which are associated with good or adverse results. FUSAM addresses this question.

1.5.3 Is there potential for RUTF enhanced by functional food to improve TFP outcomes?

There is increasing international interest in the claim of 'functional foods' to confer "health benefits beyond the provision of essential nutrients."[54],[55],[56],[57]. The PRONUT sub-study explores the effect of:

- Probiotics - "A preparation of, or a product containing, viable, defined microorganisms in sufficient numbers, which alter the microflora in a compartment of the host and by that exert beneficial health effects."[58]

and

- Prebiotics - "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon."[58].

Recognising different but potentially synergistic effects, preparations of pre and probiotics together are termed "Synbiotics"[58].

For some conditions like diarrhoea, evidence of functional food effect is strong and based on high quality evidence, notably meta-analysis of randomized controlled trials[59],[60]. Most research however focuses on high income developed countries - where product sales are high, some $16 billion USD per year for probiotics alone[61]. Few studies are set in low income developing nations - where it is SAM and preventable mortality that are high[62]. This represents

an important research gap. There are several reasons, all underpinning the PRONUT study, why functional foods may have a role in the treatment of SAM:

i) Likelihood of benefit via known mechanisms of action

In other patient groups, probiotics and prebiotics are known to have several effects, including:

- Probiotics preventing diarrhoea (reducing incidence): in 2006 meta-analysis, diarrhoea of diverse causes was reduced by 34% (95% CI 8% to 53%) and antibiotic associated diarrhoea by 52% (95% CI 35% to 65%)[60].
- Probiotics for treating diarrhoea (reducing adverse impact and prevalence): the authors of a 2004 Cochrane review concluded that "Probioics appear to be a useful adjunct to rehydration therapy in treating acute, infectious diarrhoea" [59]. The evidence underpinning this statement was: reduced risk of diarrhoea at 3 days (relative risk 0.66, 95% CI 0.55 to 0.77); reduced duration of diarrhoea by a mean of 30.5 hours (95% CI 18.5 to 42.5 hours).
- Prebiotics can promote a healthy gut flora: encouraging the growth of 'good' organisms and competitively excluding potentially pathogenic ones[63];
- Probiotics can directly and indirectly modulate the immune system[64]. They do this at 3 levels: general (producing nutrients and anti-oxidants); humoral (stimulating IgA production; inhibiting IgE production; modulating cytokine responses); cellular (stimulating macrophage and natural killer cell function and promoting growth and regeneration)

It is biologically plausible that these benefits shown in other patient populations would also apply to children with SAM. The actions are certainly relevant to SAM, in which the following are common problems:

- impaired gut function, manifest as diarrhoea and malabsorption[65],[66];
- small bowel overgrowth[67];
- increased intestinal permeability[68],
- enteropathy[69];
- gram negative (enteric) bacteraemia[70],[71];
- suboptimal immune response[72],.

ii) Potential for public health impact

Because CMAM programmes focus on high coverage[34] improved RUTF with even modest benefits to individual patients could translate to very substantial impacts at public health level.

iii) Concerns about probiotic use in immune compromised populations

Because of the small risk of probiotics causing invasive infection[73], caution is sometimes recommended in immune compromised patients[74]. Better risk-benefit data is vital: the most vulnerable, most immune-suppressed children with SAM[75] and with HIV[76] are also those most needing therapeutic improvements.

iv) *Availability of a 'delivery vehicle' for functional additives: Ready-to-Use Therapeutic Foods (RUTF)*

RUTF is a high energy, nutrient dense paste, formulated to WHO standards for the treatment of SAM[41]. It is used in almost all CMAM programmes. As the product is manufactured in food processing factories and packaged in hermetically sealed containers, inclusion of functional additives to the standard RUTF recipe can be readily achieved and has potential for large-scale rollout in feeding programmes.

Chapter 2
Aims & Objectives

2.1 Hypotheses

In the two studies described in this thesis, two key factors influencing SAM mortality in a treatment programme are explored:

i) Treatment efficacy

Therapeutic food is a key intervention in a treatment programme for SAM. Improved therapeutic food therefore has the potential to improve outcomes.

Hypothesis arising:

i. In an HIV prevalent setting, addition of a pre/probiotic functional food (Synbiotic 2000 Forte™) to a standard diet of Ready-to-Use Therapeutic Food (RUTF) will improve outcomes from an episode of SAM.

ii) Patient characteristics

If intervention efficacy is held constant or cannot be further enhanced, programme outcomes might still be improved by addressing patient-related risk factors. Understanding the impact of characteristics like nutritional status at admission, clinical status, family and socio-economic status will enable future programmes to better plan and respond to patient needs.

Long term outcomes are of particular relevance since these best reflect the true public health impact of treatment. (i.e. minimizing *long term* mortality and morbidity are the most important programme goals but may not necessarily be reflected by short term, in-programme outcomes)

Hypotheses arising:

i. Short term and medium term outcomes, as routinely reported by therapeutic feeding programmes, adequately reflect long term outcomes following an episode of SAM

ii. Post-SAM catch up growth is complete and comparable to family (sibling) controls

iii. **a.** Common risk factors underlie both short and longer term mortality

b. Access to post-SAM treatment services (supplementary feeding for all children and TB / HIV services as clinically indicated) is associated with improved long term outcomes

2.2 Aims & Objectives

2.2.1 Study 1 – **PRONUT** (Pre and **PRO**biotics in the treatment of severe acute mal**NUT**rition)

Aim

To determine the efficacy of a probiotic/ prebiotic functional food (Synbiotic2000 Forte™) for improving clinical and nutritional outcomes from SAM in a HIV prevalent setting

Objectives:

To determine whether addition of Synbiotic 2000 Forte™ to a standard Ready-to-Use Therapeutic Food (RUTF) diet will result in:

i. A greater proportion of children achieving nutritional cure following SAM
ii. Reduced mortality from SAM
iii. Improvements to other programme-relevant clinical and nutritional outcomes:
    a. less readmissions; less nutritional failures
    b. improved weight gain;
    c. shorter length of stay in-programme;
    d. less diarrhoea and other clinical problems

2.2.2 Study 2 – **FUSAM** (Long term **F**ollow-**u**p after an episode of **S**evere **A**cute **M**alnutrition)

Aim

To describe long term (≥ 1 year post-discharge) mortality & morbidity following an episode of SAM

Objectives:

i. To describe the occurrence and timing of in-programme and post-treatment deaths following an episode of SAM
ii. To describe the extent of catch-up growth in the year following an episode of SAM
iii. To identify risk factors for mortality from SAM:
    a. Risk factors at original admission
    b. Risk factors related to post-SAM care
    c. To determine whether risk factors for short term mortality are similar to those for late deaths

Chapter 3
Setting, participants & methods

3.1 Setting

3.1.1 Malawi, the warm (but malnourished) heart of Africa

The research described in this thesis was set in MOYO (= 'life' or 'health' in the local language, Chichewa) therapeutic feeding ward, Queen Elizabeth Central Hospital, Blantyre city, Blantyre district, Malawi. Malawi is a densely populated, landlocked country whose 2008 GDP per capita of $800 (purchasing power parity basis) ranks it 220th of 229 countries[77]. Of 13.9 million people, 85% live in rural areas and work predominantly as smallholder farmers[78]. Climate is sub-tropical with a rainy season lasting from approximately November to May each year. The staple crop, maize, is planted near the beginning of the rains and harvested around the time rains end.

Often and aptly described as "The Warm Heart of Africa", Malawi also has a less welcome reputation for high prevalence of malnutrition. The 2004 Demographic & Health survey reports:

- 22% of under-5 children are underweight
- 48% of under-5 children are stunted
- 5.2% of under-5 children are wasted & 1.6% are severely wasted

Consistent with this poor nutritional status, under-5 mortality is 133/1000 live births.

The number of children affected by SAM regularly peaks during the rainy season (also the 'hungry' season) when:

- many families have to ration what little food is still left over from last year's harvest.
- incidence and prevalence of water related diseases like malaria and diarrhoea peaks.

Together, these result in adverse nutrition-infection interactions[79] and exacerbate already prevalent background malnutrition.

Picture 5 Map of Malawi, showing Blantyre

3.1.2 Therapeutic Feeding Programmes in Malawi

For many years, Malawi had a network of about 92 NRU-style inpatient therapeutic feeding programmes. A poor harvest in 2001 was one of several factors resulting in a 2002 'famine'[80]. This renewed focus on tackling SAM.

In 2003, new national guidelines were developed, based on the WHO(1999) NRU model of care. Ministry of Health, UNICEF and international NGO Action Against Hunger were key players in a major national strategy of guideline dissemination, training and quality improvement.

Around 2003, some of the earliest community-based approaches to SAM were also being developed in Malawi. A locally manufactured RUTF had been successfully produced and validated – two key projects actually based in MOYO[81],[82]. Operational research in central region was pioneering the outpatient-based model of care central to CMAM[83]. This growing evidence-base, backed by inspired national and international leadership, resulted in Malawi being one of the first countries to adopt a national CMAM strategy[25].

The shift from NRU-style to CMAM-style TFPs led to many programmes having to adapt and evolve. MOYO was among those changing its approach to SAM. It illustrates a typical transition process:[84]

- Up to 2003, care was fully inpatient based;
- In mid 2003; outpatient-based rehabilitation began, but with children returning to MOYO rather than to a local OTP for review and RUTF collection;
- Just prior to this PhD, RUTF replaced F100 milk in transition phase.
- In mid 2008, (after PRONUT had finished but whilst long term FUSAM visits were still under way) a full CMAM programme began in Blantyre district, continuing the transition towards outpatient / public health focused treatment.

3.1.3 MOYO nutrition ward, Department of Paediatrics, Queen Elizabeth Central Hospital, College of Medicine, Blantyre.

'Moyo' nutrition ward for children with SAM is one of several paediatric wards of Queen Elizabeth Central Hospital, Blantyre. Queen's is the clinical base for the College of Medicine, Malawi's only medical school. As a teaching hospital, Queen's is also a tertiary referral centre. However, though the clinical and diagnostic expertise is greater than elsewhere in the country, there is not always significantly more that can be offered in terms of medical treatments. Certainly for SAM, the clinical caseload is thus more typical of a large district hospital than a tertiary referral centre[†]. According to the 2008 National Census, the district served comprises an:

- Urban Blantyre population of 661,444
- Rural Blantyre population of 338,047

The network and distribution of health centres in Blantyre district is shown opposite. Two also have attached inpatient NRUs which share the SAM caseload with MOYO. Numbers admitted to these are small in comparison.

Most malnourished children present either direct to Queen's or arrive via local health centres after initial assessment by community-based health workers.

Queens and Moyo are part of the government health service and all services are provided free of charge.

Figure 7 - Map of health centres and their catchment areas in Blantyre district

(source: M.Kerac, from ArcView files obtained from the Malawi National Spatial Data Centre, Lilongwe)
The approximate area of urban Blantyre is outlined in grey.
Approximate scale of this map at the widest points is 80km North-South and 40km East-West

[†] The only exception to this are very small numbers of post-surgical patients referred to MOYO for nutritional support.

3.2 Study participants: the MOYO case definition of SAM

All patients admitted to MOYO nutrition ward were eligible for the PRONUT study and later for FUSAM. Following Malawi National Guidelines[25] and consistent with international guidelines[9], the MOYO admission criterion and case definition of SAM was:

- Weight-for-height <70% of median (NCHS reference)

or

- Mid-Upper Arm Circumference (MUAC) <11cm

or

- Kwashiorkor (oedematous malnutrition)

CMAM was only started in Blantyre district in 2008, so the distinction into complicated or uncomplicated SAM was not applicable. All patients identified as having SAM were admitted for initial inpatient treatment (see discussion, chapter 6 for generalizability implications). Also sometimes admitted were a small number borderline SAM cases: mostly high risk children such as those rapidly dropping down growth chart centiles or HIV positive and sick.

Picture 6 MOYO nutrition ward, Queen Elizabeth Central Hospital, Blantyre, Malawi

3.3 Study participants: the MOYO patient care pathway

3.3.1 Admission routes to MOYO

All children presenting to Queen's hospital were first seen in the Accident and Emergency (A&E) area. Here they were assessed, triaged and referred according to clinical indication:

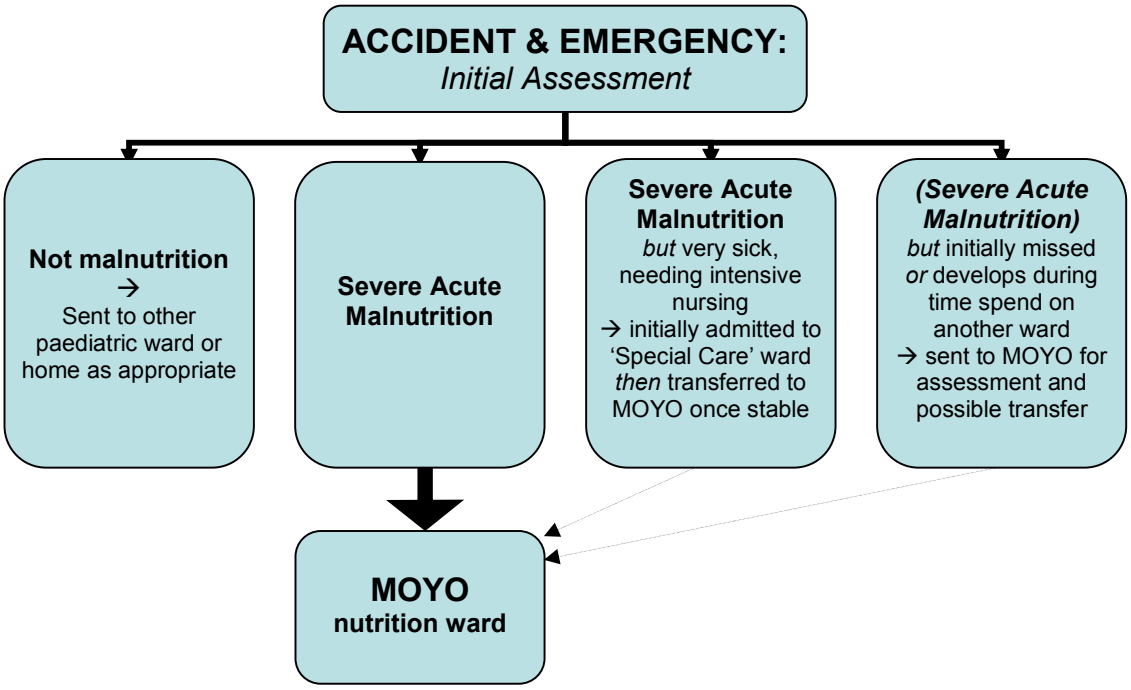


Figure 8 Admission routes to MOYO nutrition ward

The thick line represents how most children are admitted to MOYO, dotted arrows represent occasional cases

Initial assessment in A&E included routine weight and clinical assessment, looking specifically for oedema or visible wasting. Most SAM was thus identified and referred direct to MOYO. Borderline cases of possible SAM were frequently sent to MOYO for definitive assessment: weight-for-height, MUAC and oedema. Small numbers of patients arrived on MOYO via other paediatric wards.

3.3.2 Initial assessment and treatment in MOYO (including anthropometry)

This comprised:

i) Anthropometry

Measurement of weight, length and MUAC followed research standards[85]. (see **3.6.1** for details)

ii) Clinical assessment

Every patient was assessed by a MOYO clinician as soon as possible after admission. If admitted out-of hours, core details would be taken by the nurse in-charge or on-call doctor and full details

completed the next day. This allowed important urgent treatment to be started immediately (e.g. second or third line antibiotics)

iii) Early feeds whilst awaiting assessment

All children arriving on MOYO would be given an early feed of F75 milk. This was to minimise any risk of hypoglycaemia whilst awaiting assessment and admission to the main ward.

3.3.3 Inpatient treatment

This comprised two main treatments delivered in parallel according to clinical indication:

a) Nutritional treatments

The quantity of therapeutic feeds, both milk and RUTF was adjusted according to the child's weight using standard charts in the national guidelines.

i) Stabilization phase (Phase 1)

All children were initially fed F75 therapeutic milk given every 3 hours, including overnight. This "stabilization" phase lasted a minimum of 1 night.

ii) Transition phase (Tr)

Criteria for progression to transitional feeds were clinical improvement and return of active appetite, defined as easily finishing the prescribed volume of F75 milk (as reported by main carer).

Consistent with new CMAM guidelines[37] but slightly different to WHO guidelines (which recommend F100 milk for transitional phase), Ready-to-Use Therapeutic Food (RUTF)[41] was introduced to the diet at this stage. A full RUTF prescription provided 200 kcal energy, per kg body weight, per day. For a 7 kg child (median NRU admission weight) this was approximately 300g RUTF/day. Recognising that not all children would be able or physiologically ready to eat the entire RUTF target amount at this stage, F75 was continued. Mothers were instructed to give initially small amounts of RUTF (e.g ½ teaspoonful every 3 hours, alongside the milk ration) and to gradually increase that amount as guided by the child's appetite. As a guide to what the full target amount should ultimately be, they were each given a small 'ticket' with the number of RUTF pots per day pictured, plus the same amount expressed as teaspoons per 3 hours. Feeding instructions stressed that mothers should never to try to force the child to eat beyond what he/she demanded.

Similar to phase 1, Tr lasted for a minimum of 1 night. *(see appendix D for MOYO guidelines on phase progression)*.

iii) Rehabilitation phase (Phase 2)

Active appetite reflects clinical improvement and again was the main criterion for moving forwards from transition phase. When *easily* eating at least ¾ of his/her RUTF target ration, a child had by definition moved him/herself onto phase 2 and hence this was a much more child / physiologically led process - in contrast to traditional phase transition, when the in-change clinician made the decision when the child was ready to move to phase 2. As long as clinically also well at this point, the child was ready for transfer to home-based rehabilitation at the next available opportunity (discharges from the ward were done twice a week).

During phase 2, free fluids and other foods (e.g. likuni phala – a popular local brand of maize-based porridge fortified with micronutrients) were also allowed alongside the RUTF. F75 milk was stopped at this stage.

b) Clinical treatments

These were given according to clinical indication and again followed standard guidelines. At admission, all children had a PCV (packed cell volume, testing for anaemia) and thick film testing for malaria. Transfusions were rarely done: usually only in cases where anaemia was both very severe and clinically symptomatic.

All children had empirical antibiotic treatment with co-trimoxazole. In cases of presumed sepsis, 2nd or3rd line antibiotics were also used. These are described in detail in ***chapter 4.2.4***.

3.3.4 OTP (Outpatient) treatment

Once clinically well and on phase 2 feeds, children were transferred from ward-based care to outpatient care, to complete their nutritional rehabilitation at home. They took home sufficient RUTF rations and any other treatment needed (e.g. finishing a course of oral antibiotics)

At fortnightly intervals, they attended outpatient clinics at MOYO for clinical review and to collect further rations of RUTF. During the study, transport money was reimbursed to minimise defaulting.

3.3.5 Discharge from MOYO TFP

Clinical cure was defined as 2 consecutive visits above or at the target weight of 80% WHM. Minimum time spent in OTP to successful cure was thus 4 weeks (=2 fortnightly visits). On rare occasions when a patient had lost weight since last visit but was still >80% WHM, he/she would still be diagnosed cured but would be brought back for an extra OTP visit to ensure good subsequent progress.

Maximum time on OTP was 10 weeks (=5 fortnightly visits). If still below target weight (two consecutive visits at >80% WHM) by this time, a child would be deemed a 'nutritional failure' and referred elsewhere for further treatment. The commonest reason for such onward referrals was HIV or disability. In most such cases nutritional failure was expected and the patient was referred well in advance of final OTP visit so that transfer to follow-on services should be quick and smooth.

3.3.6 HIV & CD4 testing

Prevalence of HIV on MOYO was over 40%, compared to a national NRU average of 24%[86].

HIV counselling and testing was considered a key element of good patient care and was a routine part of ward protocols. An opt-out policy was operated whereby all patients and their carers were offered a test as soon as the child was stable enough to visit the upstairs office where testing was done. This service was provided by a dedicated team separate to MOYO clinical and study staff.

Testing protocols involved two ELISA rapid tests (Determine® and Uni-Gold™), with a third (Hema Strip™ or SD-Bioline) for discordant results. With carer consent, results were stamped in patient notes and made available to the clinical team in order to guide treatment and facilitate further referrals as needed. PCR for definitive diagnosis in children <18 months of age was unavailable. In such cases, cotrimoxazole antibiotic prophylaxis was always started on a presumptive basis if a child was ELISA seropositive. Advice was given about the need for repeat testing at >18 months age to get a definitive diagnosis. More complex clinical decisions - such as whether to start antiretroviral medication - were made on a case-by-case basis. This happened if other problems such as TB had been excluded or treated yet a child continued to deteriorate. The timescale for such interventions was almost always after the patient had been discharged from

MOYO care. Hence it was not relevant to PRONUT results and only relevant to very small numbers of children in the FUSAM study.

In around November 2006, CD4 testing became available via a separate project running in MOYO ward. Being part service provision, part operational research to help guide appropriate referrals to HIV-related treatments, only HIV positive patients were tested. Testing was done at the first outpatient visit so that results would be back for the second visit. Patients who died before first visit would thus have no CD4 result available.

3.3.7 HIV treatment

The key reason for opt-out testing of children and carers was to facilitate timely referral to HIV treatment services. HIV seropositive patients were treated according to national protocols. These included referral for antiretroviral (ARV) medication based on clinical staging criteria (notably persistent malnutrition despite treatment) and CD4 count if available. An ARV waiting list at the time of the PRONUT study meant that additional inputs rarely started during initial nutritional treatment.

All HIV positive patients were started on long term co-trimoxazole prophylaxis as soon as diagnosed.

3.3.8 Other TFP-related services: SFP, TB, disability

Keeping patients monitored and acting as a safety net to prevent nutritional relapse, all patients discharged from MOYO were referred to their nearest supplementary feeding centre for a further 4 months supplementary feeds. These were located at health centres distributed throughout the district. SFP programmes used fortified corn-soy blend.

Other common referrals from MOYO were to TB and disability services. These gave specific support and treatment following relevant protocols.

3.3.9 Patient flow summary & cohorts enrolled in PRONUT & FUSAM

The flow chart on the next page summarises patient flow through the SAM treatment programme. Possible outcomes at each stage are shaded light blue. PRONUT focuses on medium term outcomes as reported by most field programmes. FUSAM describes long term outcomes from the whole cohort of patients originally admitted to the ward.

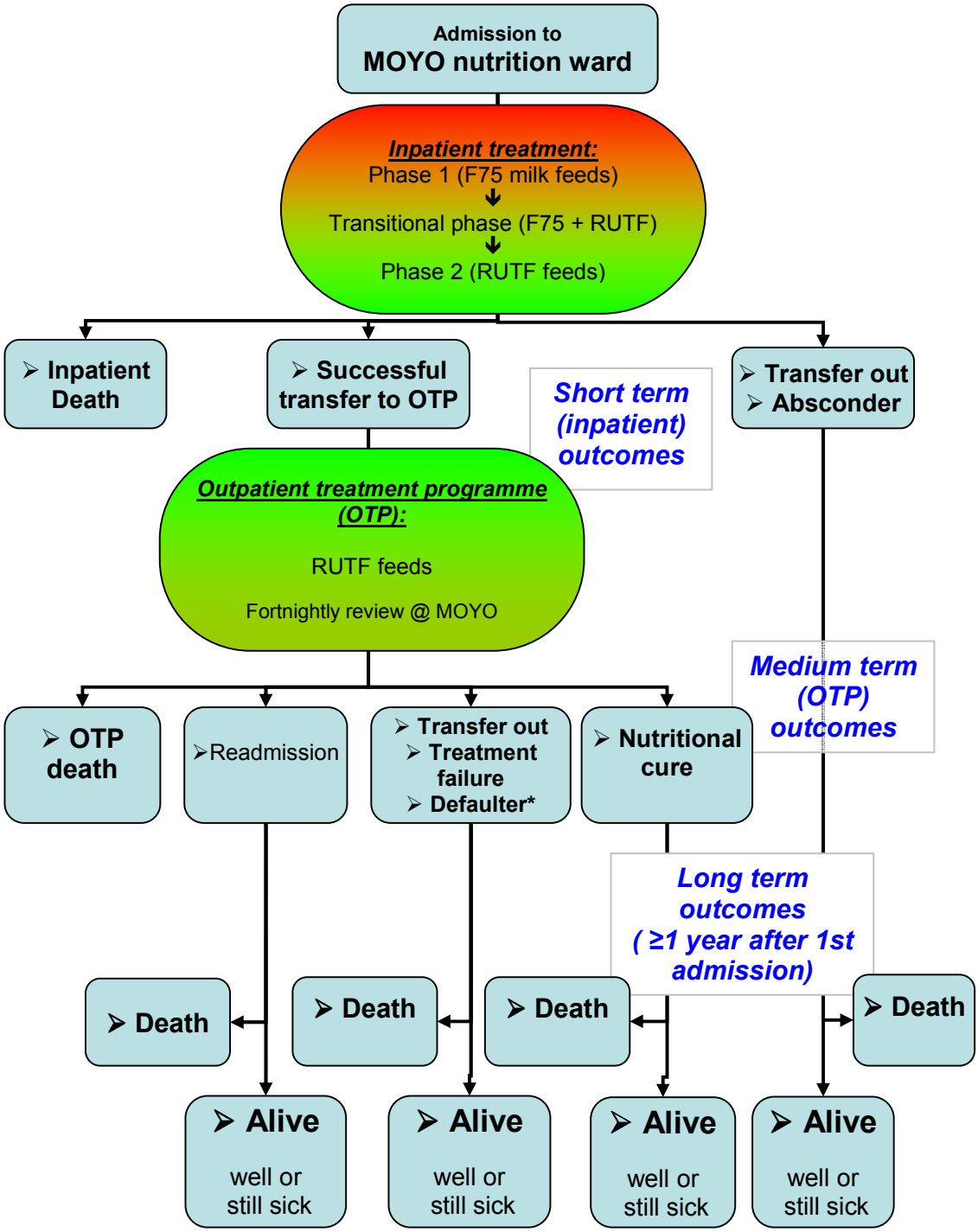


Figure 9 Flow chart overview of SAM treatment with short, mid and long term outcomes

* Default is frequently cited by field programmes, but it is not definitive in the same way other outcomes. It is the outcome cited when no other can be determined. Common reasons for default include death or clinical improvement, so that the carer perceives no reason to return for further formal follow-up.

3.4 Methods: quality control systems

Several aspects of study methodology are specific to either PRONUT or FUSAM and are described in their respective chapters. Common to both studies are quality control systems described here:

3.4.1 Anthropometry

High quality anthropometry is important for nutrition-focused research. For both PRONUT and FUSAM the following equipment was used and measures taken to optimise data quality:

a) Weight measurement - scales

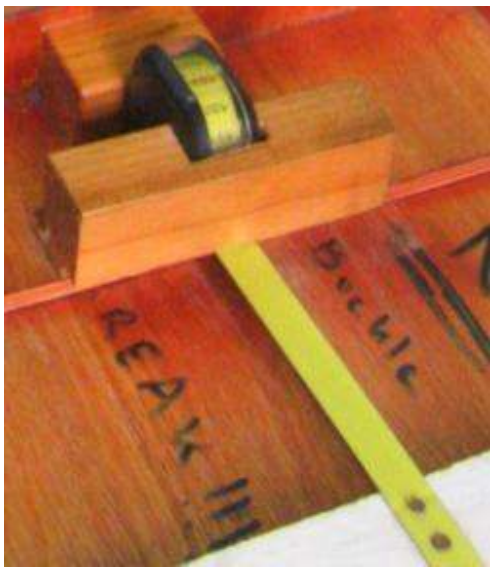
Children were weighed naked (or with underclothes only for older children) on Tanita 1582 digital scales accurate to 20 grams. These were portable enough for inpatient and OTP use in PRONUT and also for field-based measurement in FUSAM. Calibration was checked every day using 2.3kg and 5kg reference weights.

b) MUAC measurement – insertion tape

MUAC was measured to the nearest 1 mm using insertion tapes procured by UNICEF. The same tapes were used for both PRONUT and FUSAM.

c) Length/height measurement – length/height boards

For PRONUT, this was measured to the nearest 1mm using specially adapted locally made length boards (see picture below – the tape measure has a clear window with red line marking exact length). For simplicity, only length was measured for all children. In the final study database children >2 years (whose reference tables are based on height), the length measurement taken on MOYO was converted to height by subtracting 0.5cm[15].



Picture 7 MOYO length board

The MOYO height board was not portable and could not be used for FUSAM field visits. For these, a "Leicester Height Measure" (Harlow Healthcare) accurate to the nearest 1mm was used to measure standing height for children ≥2 years. Lengths of children <2 years old was measured using a Dunmow length mat (Harlow Healthcare). Data collection forms noted whether length or height was measured and where needed corrections could be made.

d) Age assessment

Age is a key independent variable, and is also critical to calculating anthropometry z-scores. To minimise errors, study questionnaires asked age and date of birth as separate questions. If answers were inconsistent, further details could be asked and true age determined with greater accuracy.

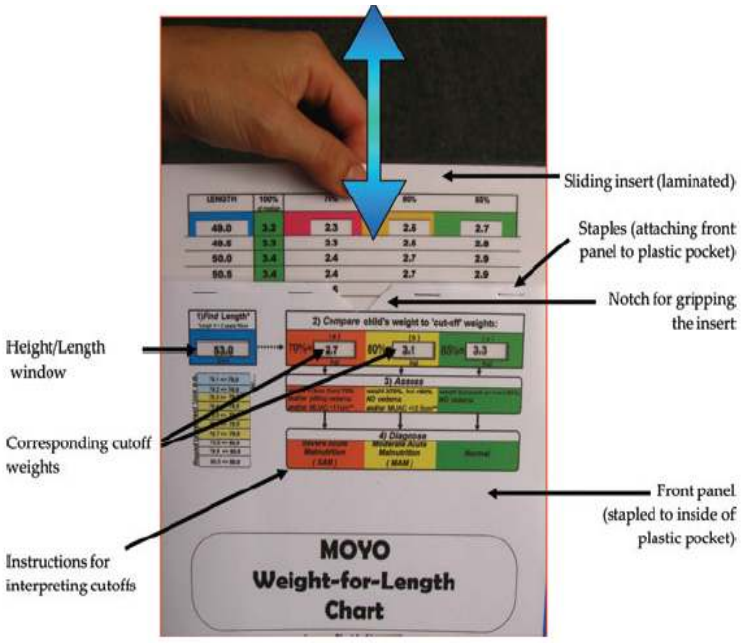
e) Repeat measurements

PRONUT followed research standard protocols whereby trained observers measured in pairs[85]. If within set agreement limits, the mean of the two measurements was taken as correct. Otherwise, both observers would re-measure until their agreement was acceptable. Criteria for repeating were:

- Their two MUAC measurements differ by >5mm
- Their two length measurements differ by >7mm
- The measured length decreased since last measurement
- Length or MUAC increased by >20mm since last visit

f) The MOYO chart

To aid correct classification of weight-for-height/length into SAM or non-SAM, a low cost "MOYO" slide chart was developed[87]. This replaced the traditional weight-for-height/length lookup table and is described in detail in appendix K (PhD Research articles). One feature of the MOYO chart was a focus on target weights for discharge rather than overly frequent weight-for-height/length recalculations.



Picture 8 The MOYO chart

3.4.2 *Patient records systems*

To enhance both study and routine data quality, several modifications were made to MOYO's patient records systems. These included:

- More detailed entries to admissions and outpatient registers;

These provided information backup in case of lost files and also facilitated quick cross-checking as needed (e.g. to identify details of a previous admission).

- Training and supporting MOYO staff on the importance of good data management;
- Filing patient notes by sequential admission number rather than discharge date as had previously been done. This change alone was a key factor in low losses to follow-up for both PRONUT and FUSAM. Filed according to the new system, it was much easier to identify missing files; easier to refer to previous admission episodes; easy to find and organize old notes for FUSAM long term follow-up.

Picture 9 (right) The purpose made filing system for MOYO patient records.

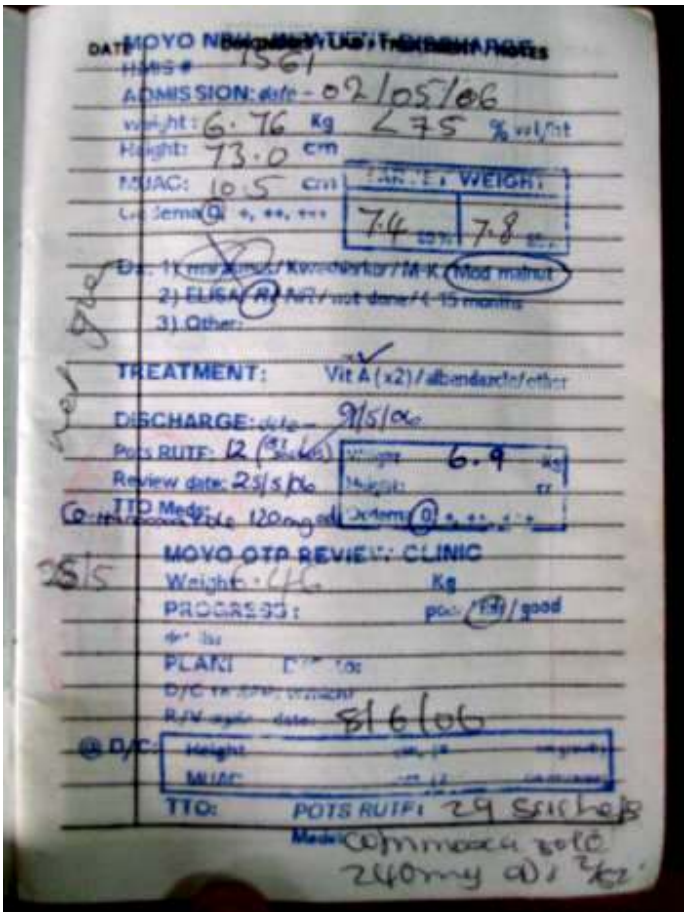
Folders were colour coded: blue for PRONUT patients; yellow for those not enrolled in PRONUT; red for inpatient deaths; orange for outpatient deaths. For data protection, the cabinets were locked and kept on the ward.

Pictures 10 (above) Old filing system – by discharge date

Picture 11 (right) New filing system – by admission number

3.4.3 Patient held records

All children in Malawi were expected to have a health passport documenting health events such as immunizations, growth and clinical visits. Use was made of this 'health passport' to document routine MOYO care. A rubber stamp (see below) was designed to enable key information to be easily and quickly recorded: admission anthropometry; admission diagnosis; target weight; HIV status (coded as "ELISA" R(eactive) or NR(non-reactive)) to protect privacy whilst simultaneously ensuring clinicians were aware and could thus offer appropriate treatments); details of other relevant conditions such as TB; details of progress at OTP review clinics; details of treatments given.



Picture 12 MOYO stamp in patient-held health passport

Whilst designed to enhance routine clinical care, the MOYO stamp also benefitted quality of research data by 'backing up' key information and enabling cross checks to be made when recording patient id number or anthropometry on separate study paperwork.

3.4.4 Staff training and supervision

The budget for PRONUT included funding for extra clinical staff. These included: 1 clinical officer; 2 nurses; 1 homecraft worker (responsible for therapeutic food preparation); 3 patient attendants (secondary school graduates responsible for detailed completion of study questionnaires as well as general ward tasks). Staff received training prior to study start and helped feed back on pilot versions of the study forms. All were expected to contribute to routine ward duties alongside other members of the MOYO team. They alone however were responsible for study-related paperwork and anthropometry measurement. During the study, they were directly supervised by MK, the

study principal investigator. Study forms were regularly checked. Problems or inconsistencies were identified and discussed with the responsible staff member.

FUSAM fieldwork was done by 3 senior nurses, supported by the study driver. This meant that appropriate clinical assessment, advice, and where necessary simple immediate treatment could be given. It was as important that these visits be of clinical benefit to the patient as of research benefit to the study. Again all 3 nurses had regular clinical duties and had a rota to take time off to do FUSAM visits. Returned forms were checked and quality controlled by a study co-author and fellow paediatrician, GC.

3.5 Methods: the 'verbal map' and patient follow-up

Home follow-up was important for both:

- PRONUT - being able to trace defaulters and find out whether they were alive or dead.
- FUSAM - being able to determine long term outcomes.

It was made possible by using a 'verbal map' system which had been successfully used in a previous study[84]. During their original admission, consenting patients provided detailed instructions how to reach their home location. An example of a typical (fictional) map is:

> "At Bangwe township, turn left just before the Kandodo supermarket minibus stop. Go straight along the dirt road until you get to the Pentecostal Church. Just opposite the entrance of the Church there is a group of charcoal sellers. Ask them for Mr Banda, and he will show you the family home, which is just 5 minutes walk away"

Taking an effective verbal map was helped by a physical map held on the ward. This showed Blantyre district villages, trading centres and schools, and enabled staff to record a helpful description of local landmarks en route to the patients' home. Finally, some patients were given a lift home by the MOYO driver. This allowed GPS coordinates to be taken at the house, again making it possible to find the residence in the future.

Picture 13 Close up detail of the Blantyre district map used to help locate patients' home locations

Picture 14 Blantyre district map (full version)

The overlay grid helps locate the exact location of patients on the map. The large grid (visible blue lines) is 10km x 10km. The smaller grid being held up is 1km x 1km (the thin lines are not visible on this picture, though row numbers and column letters can be seen).

3.6 Ethical Approval

The PRONUT study was first approved by College of Medicine Research & Ethics Committee (COMREC) in 2005. Initial plans had been to base the study in a CMAM programme in central Malawi. Updates to the protocol, including the change of setting to MOYO were approved in late 2006.

FUSAM was granted initial approval as an extension to the PRONUT study in mid 2007. Final approval was granted in 2008 after UNICEF funding was confirmed

(please *see* ***appendix C*** for letters from the Ethics committee)

Chapter 4

'PRONUT' Study

4.1 Aim

To determine the efficacy of a probiotic/ prebiotic functional food (Synbiotic2000 Forte™) for improving clinical and nutritional outcomes from SAM in a HIV prevalent setting

4.1.1 Objectives:

To determine whether addition of Synbiotic 2000 Forte™ to a standard Ready-to-Use Therapeutic Food (RUTF) diet will result in:

i) A greater proportion of children achieving nutritional cure following SAM

ii) Reduced mortality from SAM

iii) Improvements to other programme-relevant clinical and nutritional outcomes:

   a. less readmissions; less nutritional failures

   b. improved weight gain;

   c. shorter length of stay in-programme;

   d. less diarrhoea and other clinical problems

*(please see also **chapter 2**, for underlying rationale and hypothesis)*

4.2 Methods

4.2.1 Study design

PRONUT was a double blind, randomized controlled efficacy trial.

4.2.2 Setting & participants

MOYO nutrition ward and its patient profile has been described in ***chapter 3*** of this thesis. All children admitted to MOYO were eligible for recruitment following written informed consent

To detect a possible subgroup effect, we made a-priori plans for a major secondary analysis. This subgroup excluded small numbers of children aged <6 or >60 months[88]; those with very low weight (<4kg); cerebral palsy; an obvious dysmorphic syndrome; SAM secondary to major surgical problems; moderate acute malnutrition (MAM) with complications. Uniting this subgroup was a plausible biological reason why each 'type' of child may not respond so well to a feeding-centred intervention - e.g. children with disabilities often have growth curves different to those of their peers[89]. The age range was chosen so as to be consistent with standard nutrition reporting and thus comparable with other studies. The 4kg cut off is often used as a proxy for age <6 months so again was excluded here for comparability with other studies[90].

Another secondary analysis explored a post-hoc hypothesis that Synbiotic benefits would be greatest in children during the outpatient phase of SAM treatment. This did not arise from multiple 'data trawling' post-hoc analyses, but follows logically from the original version of the PRONUT protocol. PRONUT was originally designed in 2004 and was initially set in Dowa district, Malawi which has an outpatient-based CMAM-style therapeutic feeding programme. In the original protocol, only outpatients were to be recruited. At the time, this equated to RUTF feeds (inpatient rehabilitation care used mainly F100 therapeutic milk). Due to logistical issues, the study was moved to its actual location of Moyo ward, Blantyre, in late 2005. By 2005, RUTF was increasingly used during final stages of inpatient care, as well as during outpatient care. This evolution of routine practice led to decision to randomize during latter stages of inpatient care rather than at entry to outpatient care.

4.2.3 Interventions

As described in ***chapter 3***, treatment on MOYO followed Malawi National Guidelines for the Management of Acute Malnutrition[25]. All children were initially fed "F75" therapeutic milk. PRONUT began when a child progressed to "rehabilitation" phase feeds. Criteria for progression were clinical improvement and return of active appetite (easily finishing the prescribed volume of

F75 milk). Ready-to-Use Therapeutic Food (RUTF)[41] was introduced into the diet at this stage. RUTF prescriptions provided 200 kcal energy, per kg body weight, per day. For a 7 kg child (median NRU admission weight) this was approximately 300g RUTF/day.

Control children received standard RUTF. The intervention group received RUTF with added Synbiotic2000 Forte™ (Medipharm AB,Kågeröd, Sweden). This had been proven effective in other studies in other patient groups[91, 92] and as described in ***section 1.5.3*** also therefore had potential for useful effects in SAM. Freeze-dried Synbiotic powder was factory-mixed into RUTF at a weight ratio of 1:50. Batches of control RUTF were always made prior to batches of intervention RUTF to prevent cross-contamination. Synbiotic constituents were:

i) Four different probiotic lactic acid bacteria (LAB): (10^{11} colony forming units, CFU of bacteria total)

~ *Pediococcus pentosaceus* 16:1 LMG P-20608;

~ *Leuconostoc mesenteroides* 23-77:1 LMG P-20607;

~ *Lactobacillus paracasei subsp paracasei* F-19 LMG P-17806

~ *Lactobacillus plantarum* 2362 LMG P-20606

ii) Four prebiotic fermentable bioactive fibres: (2.5g of each per 10^{11} bacteria)

~ Oat bran (rich in β-glucans); inulin; pectin; resistant starch

For quality control, randomly selected samples of RUTF were regularly sent to Medipharm's laboratories in Sweden within a week of manufacture and again after 2 months storage at local ambient temperature in Malawi. Medipharm's microbiological culture results showed that intervention RUTF consistently contained >$1x10^8$ CFU of lactic acid bacteria per gram of RUTF. This equates to a prescribed average dose of >$1x10^{10}$ CFU organisms per patient per day (please see ***appendix F.1*** for details)

Outpatient therapeutic feeding

Once clinically well and easily finishing at least ¾ of their daily RUTF ration, children were transferred from inpatient care to outpatient treatment, to complete their nutritional rehabilitation at home. They continued original group allocations of either control or Synbiotic-enhanced RUTF. RUTF prescriptions remained at 200 kcal energy, per kg body weight, per day. At fortnightly intervals, children attended outpatient clinics for clinical review and to collect further rations of RUTF.

4.2.4 Trial Safety & Sepsis monitoring

RUTF safety and quality control

The Valid Nutrition RUTF factory in Lilongwe, Malawi (which supplied this study and mixed the Synbiotic into intervention RUTF) was licensed for the manufacture of food products. RUTF samples were regularly monitored by the Malawi Bureau of Standards for:

- Conformity to product specifications (macronutrient profile within range; water content sufficiently low – please see ***table 3,*** *RUTF nutrient profile*)
- Microbiological safety
- Aflatoxin (levels within safe limits)

Data Safety & Monitoring Board (DSMB)

To monitor trial safety, an interim analysis reviewed the main outcomes, % cure and % deaths. Early Stopping criteria were group differences exceeding the Peto-Haybittle rule ($p<0.001$), or serious adverse events[93]. Neither occurred.

Probiotic related sepsis & antibiotic regimes

On admission, all children routinely started a 7 day course of co-trimoxazole antibiotics. Dose was 120mg twice a day (bd) for children weighing <10kg; 240mg bd for children 10-25kg and 480mg bd for those >25kg. HIV seropositive children were continued on long term daily prophylaxis (dose 120mg co-trimoxazole once a day (od) for children <10kg; 240mg bd for children 10-25kg; 480mg bd for those >25kg). According to clinical need, some also received parenteral 2nd or 3rd line antibiotics. Standard 2nd line regime was chloramphenicol and gentamicin. 3rd line was ceftriaxone or ciprofloxacin plus gentamicin.

In cases of presumed sepsis in a sick child, a blood culture was taken. To identify possible probiotic sepsis we developed additional microbiology protocols involving culture on MRS agar (Oxoid Ltd, Cambridge, UK) and subsequent bacterial subspecies identification (***figure 10*** and ***appendix F.2)***. These were never needed as no suspicious organisms grew at the initial culture stage.

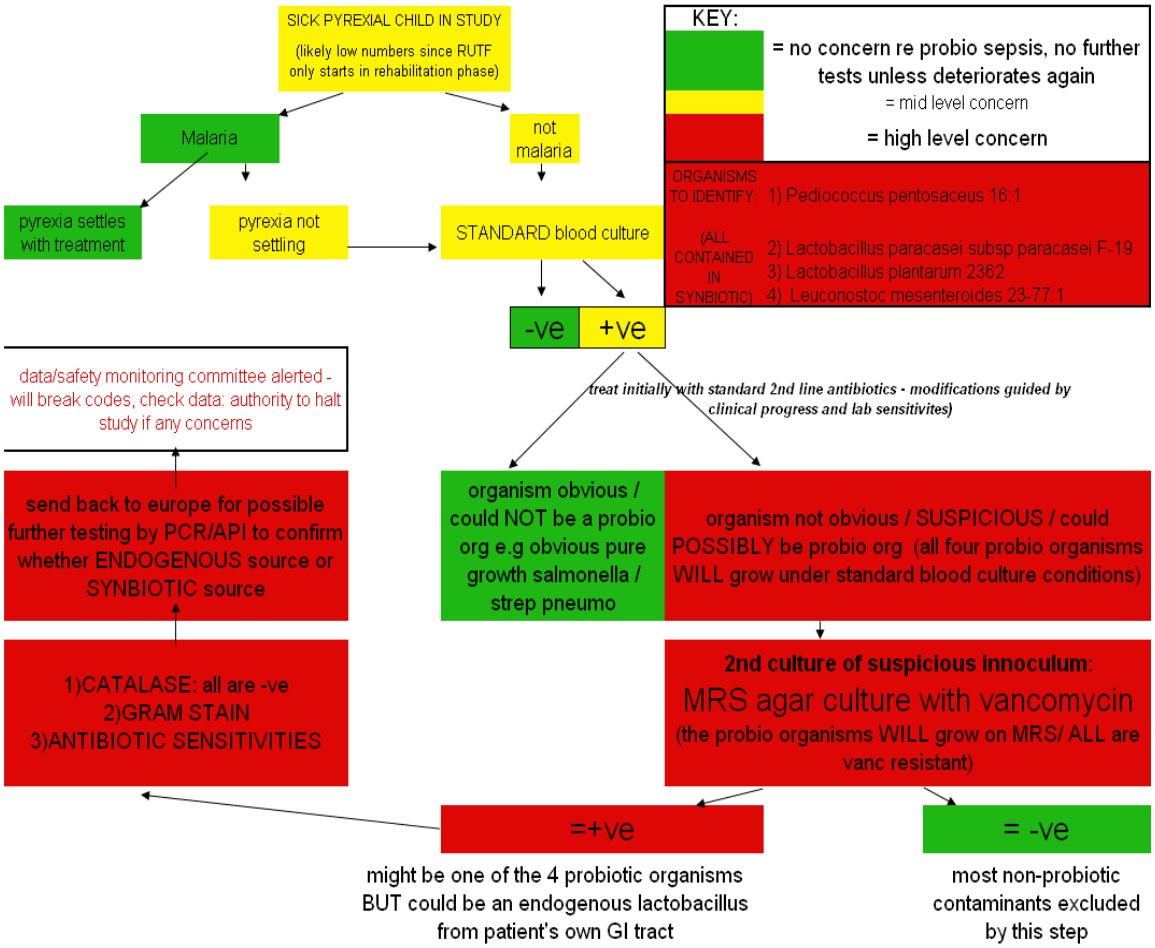


Figure 10 Identification of possible probiotic associated sepsis

4.2.5 Outcome variables

PRIMARY OUTCOME was % of children achieving nutritional cure. This was defined as two consecutive outpatient visits, a fortnight apart, with weight-for-height ≥ 80% of median (NCHS reference)

SECONDARY OUTCOMES were:

i) Routine nutrition programme performance indicators: [88],[37]

- ***Death rate (%)***
- ***Default rate (%)*** ~ defined as missing two consecutive outpatient visits (approximately 4 weeks without contact). Defaulters were followed up by a mobile team. Deaths at home were classed as outpatient deaths.
- ***Nutritional failure rate (%)*** ~ defined as not achieving cure despite 5 visits (approximately 10 weeks) of follow-up. Failures (most commonly due to underlying HIV) were referred for further care, including to anti-retroviral (ARV) services.
- ***Readmissions to hospital (%)***
- ***Maximum weight gain (g/kg/day)*** ~ calculated using minimum observed inpatient weight as the baseline weight (this is the closest approximation to 'dry weight'. It is important to note however that some children died or absconded whilst still oedematous. Rarely, some children were discharged to outpatient care despite still having some oedema: this is consistent with CMAM programmes which safely treat oedematous children at home)
- ***Length of stay in programme (days)***

ii) Carer reported clinical & progress outcomes

Trained study staff used pre-piloted, standardized questionnaires (please see ***appendix D for details of these forms***). Symptoms were reported and signs recorded daily whilst the child was an inpatient. At baseline, and at each fortnightly outpatient clinic, carers were asked about symptoms in the preceding 2 weeks.

4.2.6 Sample size

Data from 2003-4 was used to estimate baseline/control group outcomes[84] A 10% increase in cure was chosen as clinically relevant. Using α=0.05 and power of 80%, 348 patients per group were needed to detect an improvement from 65% control group cure in to 75% Synbiotic cure (StatCalc, EpiInfo v.3.3.2™, CDC, Atlanta, USA). To account for follow-up losses and ensure adequate numbers for subgroup analyses, the aim was to recruit 800 patients.

4.2.7 Randomization

Sequence generation

A random sequence representing the two study groups was computer generated independently of the field team. Permuted blocks of 50 (25 group '1', 25 group '2' per block) ensured balanced groups for interim DSMB safety analysis.

Allocation concealment

Referring to the above 'master list', an independent volunteer inserted one of two sticky labels (printed "Group 1" and "Group 2") into sealed, opaque, sequentially numbered envelopes.

Implementation

When consenting and eligible patients (those starting transitional phase feeds) went to receive RUTF for the first time, study staff would open the next numbered envelope to reveal the label concealed inside. This assigned the patient to one of the two RUTF groups. To ensure the correct group was maintained for all subsequent RUTF distribution rounds, the label was stuck in the back page of the child's health passport, which the carer held at all times.

4.2.8 Blinding

The study was double but not triple blind:

Patients

Taste, colour and texture of standard (control) and intervention (Synbiotic) RUTF were indistinguishable so patients were blind to their group allocation. A small printed label on the RUTF bottle lid was the only way to identify the correct group. At the beginning of the study, the RUTF factory manager decided independently and at random whether group "1" or "2" should contain Synbiotic.

Field Staff

Project field staff were unaware of whether group "1" or "2" contained the Synbiotic. They were also blind as to whether a patient was even group "1" or "2" when assessing or managing a particular patient. Group "1" or "2" allocation was recorded hidden inside the child health passport for the purpose of correct food distribution but nowhere else on patient or study files. Strict instructions were given that this should only be referred to by staff distributing RUTF at the end of the clinic or end of ward round

Investigators

All investigators except MK were unaware of study codes. MK was inadvertently unblinded part way into the study whilst coordinating RUTF quality control testing. I believe the study design was robust enough to prevent this causing any biases: main outcomes were hard and objective (e.g. weight, death); other staff remained fully blinded; group randomization, concealment and allocation were all independent of MK; randomization data was entered and stored independently from other databases and merged only prior to final data analysis.

4.2.9 Statistical methods & data handling

Data were entered in EpiData 3.1 (EpiData Association, Odense, Denmark, 2003-4). Simple macros ('Check' files) helped ensure high quality data entry, e.g. variables plausible, in-range and consistent with other related variables. Key data (anthropometry, dates, final outcomes, HIV status) were double entered. WHO Anthro 2005 v1 (World Health Organization, Geneva) was used to calculate anthropometric Z-scores using the NCHS reference, still current in Malawi.

Main analyses were performed using SPSSv15 (© SPSS Inc., USA). StatCalc (CDC, Atlanta, USA, 1993) and Stata Intercooled 10.0™(StataCorp LP, USA) were used for additional analyses.

Chi-square tables and approximate confidence limits for relative risk were used to examine categorical data. Normality of continuous variables was explored visually (histogram, Q-Q plots) and numerically (Kolomogorov-Smirnov and Shapiro-Wilk tests). Either independent t-tests or Mann-Whitney U tests were performed accordingly.

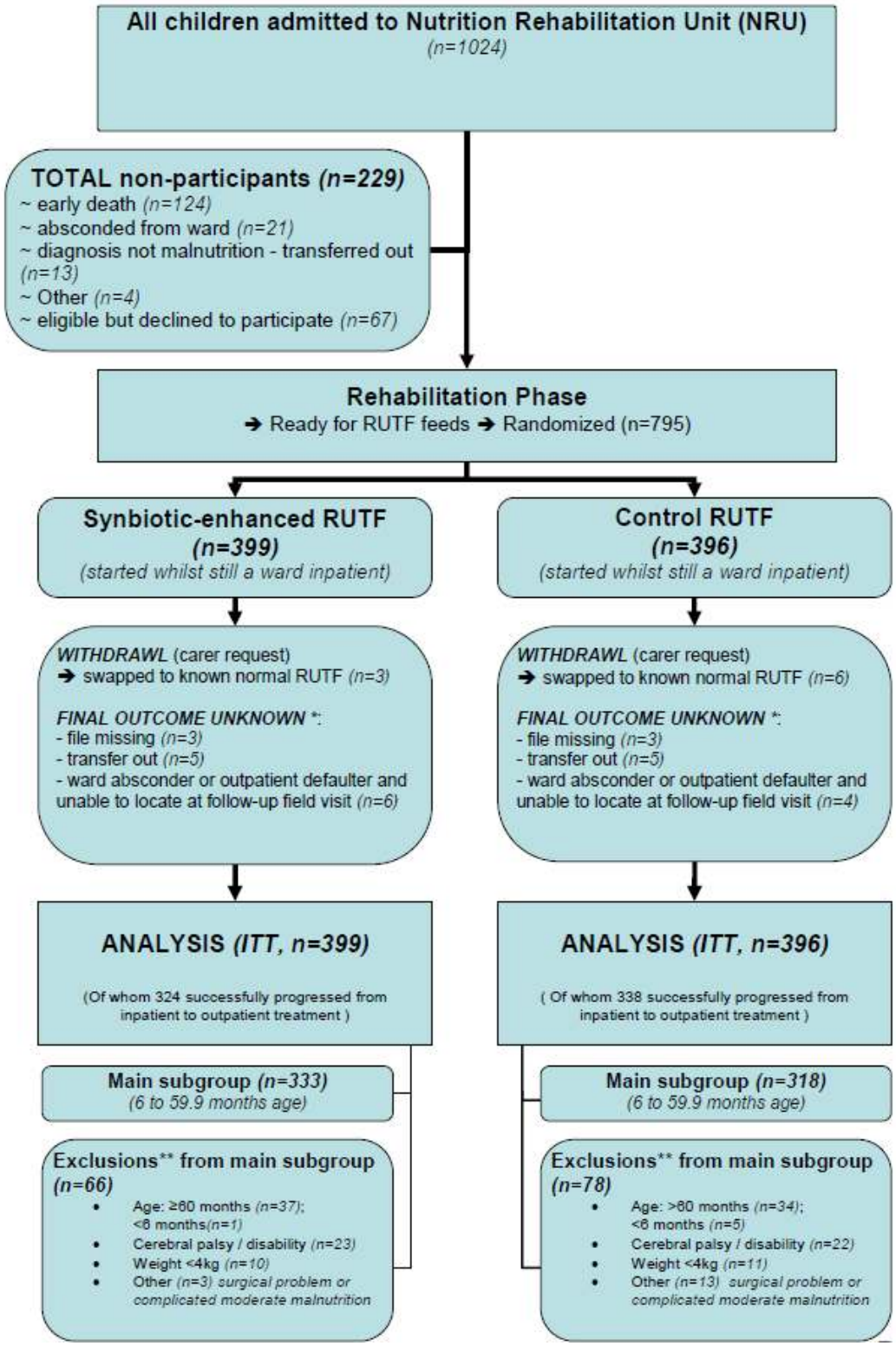
To assess the role of HIV as a possible confounder or effect modifier, all major analyses included HIV serostatus (positive or negative) as a stratification level.

Analysis was on an intention-to-treat basis.

4.3 RESULTS

4.3.1 Study flow chart

From 12th July 2006 to 7th March 2007, 1024 children were admitted to the ward. Their progress is summarized in the study flowchart below:



A total of 399 were randomised to Synbiotic RUTF and 396 to control. The commonest reason for non-enrolment was early death whilst still on stabilization phase (n=124). 67 patients declined to participate and received non-study RUTF.

4.3.2 Patient characteristics at baseline

Table 4 (supplementary tables in annexes F3 and F4) show that main patient characteristics were similar in both groups at baseline. SAM subtypes (kwashiorkor and wasting) were balanced between groups and did not affect any subsequent results. HIV serology was known for 95% of children. Sero-positivity was non-significantly lower in the Synbiotic group: 170/399(42.6%) vs. 192/396(48.5%), p=0.09. HIV status was included as a stratification level in all major subsequent analyses.

Table 4 Main baseline patient characteristics

		Synbiotic (n=399)	Control (n=396)
1) Age & Sex profile			
	Age in months *median ± IQR*	22 ± 17	21 ± 16
	Boys (%)	214/399 (53.6%)	216/393 (55.0%)
2) Nutritional Diagnosis			
	Wasting (<70% weight-for-height (NCHS) and/or MUAC <11cm, no oedema)	142/399 (35.6%)	146/396 (36.9%)
	Kwashiorkor (oedematous malnutrition)	238/399 (59.6%)	217/396 (54.8%)
3) Anthropometry (mean Z score ± sd)*			
	Height-for-Age (HAZ)	- 3.19 ± 1.5	- 3.12 ± 1.4
	Weight-for-Height (WHZ)	- 2.19 ± 1.2	-2.33 ± 1.3
	Weight-for-Age (WAZ)	-3.50 ± 1.3	-3.58 ± 1.3
	MUAC (mean cm)	11.78 ± 2.0	11.55 ± 2.0
4) Child HIV Status (%)			
	HIV seropositive	170/399 (42.6%)	192/396 (48.5%)
	HIV seronegative	203/399 (51.0%)	190/396 (48.0%)
	Not tested or unknown	26/399 (6.5%)	14/396 (3.5%)
5) Family & Socioeconomic Status			
	Main carer is mother	329/387 (85.0%)	321/384 (83.6%)
	Mother literate	246/378 (65.1%)	243/366 (66.4%)
	Household water source - piped	208/386 (53.9%)	217/382 (56.8%)
	- borehole / protected well	132/386 (34.2%)	117/382 (30.6%)
	Household toilet - traditional pit latrine	373/386 (96.6%)	367/382 (96.1%)

* Z-scores are based on admission weight rather than minimum weight unless otherwise stated.

4.3.3 Main outcomes – programme cure and mortality

Table 5 shows main study outcomes. Primary outcome, nutritional cure was 53.9% (215/399) in Synbiotic patients and 51.3% (203/396) in controls (p=0.40). Total deaths during the study period were also similar between groups: 27.1% (108/399) Synbiotic deaths vs 30.0% (119/396) control deaths (p=0.31). Other secondary outcomes were also similar. Less than 10% of patients defaulted. When followed-up in the community after 1st default episode, 19/32 (59.4%) Synbiotic defaulters and 23/36 (63.9%) controls were seen or reported to be alive and well (p=0.70). Information was unavailable for only 6/32 (18.8%) Synbiotic defaulters and 4/36 (11.1%) controls (p=0.37) who could not be located.

Table 5 Main PRONUT study outcomes

	Synbiotic (n=399)	**Control (n=396)**	**relative risk or** *mean difference (95% confidence interval)*	p
PRIMARY OUTCOME:				
1) NUTRITIONAL CURE (total)	215/399 (53.9%)	203/396 (51.3%)	**1.06 (0.93 to 1.21)**	0.40
HIV seropositive cures	66/170 (38.8%)	71/192 (37.0%)	**1.05 (0.81 to 1.37)**	0.71
HIV seronegative cures	145/203 (71.4%)	131/190 (68.9%)	**1.04 (0.91 to 1.18)**	0.59
SECONDARY OUTCOMES:				
2) DEATHS (TOTAL)†	108/399 (27.1%)	119/396 (30.0%)	**0.90 (0.72 to 1.12)**	0.31
3) OUTPATIENT DEFAULTERS or WARD ABSCONDERS	27/399 (6.8%)	36/396 (9.0%)	**0.74 (0.46 to 1.20)**	0.23
4) FAILURES OF NUTRITIONAL TREATMENT	14/399 (3.5%)	14/396 (3.5%)	**0.99 (0.48 to 2.05)**	0.98
5) READMISSIONS	27/399 (6.8%)	16/396 (4.0%)	**1.67 (0.92 to 3.06)**	0.08
6) Other: (transfers out; final outcome unknown)	8/399 (2.0%)	8/396 (2.0%)	**1.12 (0.44 to 2.86)**	0.81
7) Rate of weight gain *(mean g/kg/day ± SD)*	4.18 ± 4.0	4.14 ± 4.1	*0.04 (-0.53 to 0.61)*	0.65
8) Length of stay in programme *(median days to cure ± IQR)*	37 ± 14	38 ± 13		0.42
Outcomes stratified by treatment phase				
~ Deaths (inpatient, during 1st admission)	61/399 (15.3%)	52/396 (13.1%)	**1.16 (0.83 to 1.64)**	0.38
~ Deaths (any time during remainder of study)	47/338 (13.9%)	67/344 (19.4%)	**0.71 (0.51 to 1.00)**	0.05
total deaths during all inpatient treatment episodes (incl. readmissions)	78/486 (16.1%)	74/467 (15.9%)	**1.01 (0.76 to 1.36)**	0.93
total deaths during all outpatient treatment episodes (incl. readmissions)	30/394 (7.6%)	45/387 (11.6%)	**0.65 (0.42 to 1.02)**	0.06

† Please see table 6 for detailed breakdown of deaths according to phase of treatment.

Also in ***table 5*** are main outcomes stratified by treatment phase. There were no group differences in initial inpatient deaths (p=0.38). Deaths at any time during the remainder of the study period showed a possible trend in favour of the Synbiotic group: 47/338 (13.9%) vs. 67/344 (19.4%), p=0.05. Details of deaths during each subsequent readmission episode are shown in ***table 6***. In all, there were 486 patient admission episodes in the Synbiotic group and 467 in controls. Total deaths during inpatient care did not differ between groups (p=0.93), but total deaths during outpatient care showed a possible trend towards being lower in the Synbiotic group (p=0.06). The observed group differences were greatest:

- during the outpatient phase of the 1st admission episode: 18/324 Synbiotic deaths vs. 39/338 control deaths, p=0.006.
- among HIV seronegative outpatients (all admission episodes): 3/202 Synbiotic deaths vs. 11/194 deaths, p=0.02.

One related result not shown in table is that weight gain (g/kg/day) during outpatient treatment was no different in the Synbiotic group compared to controls (p=0.48).

Table 7 explores whether these apparent outpatient difference might be explained by group imbalances at the point of discharge from 1st admission episode to outpatient care. HIV prevalence was marginally lower in the Synbiotic outpatient group than in controls: 135/331 (40.8%) seropositive Synbiotic outpatients compared to 157/341(46.0%) seropositive controls (p=0.17). Weight-for-height Z-score (WHZ) was also different at OTP baseline, with Synbiotic mean WHZ of -2.24±1.1 against control mean WHZ of -2.44±1.1 (p=0.02).

Two points are important to note when interpreting this table:

- Nutritional diagnosis refers to that at admission and does not imply that patients were still oedematous at discharge from the ward. The great majority of children had lost all visible oedema before discharge. Only a very small number were discharged home with residual pitting (consistent with CMAM programmes which have good experience of safe outpatient treatment of clinically stable children with good appetites but minimal oedema)

Since this table excludes those patients who died during initial inpatient care, z-scores cannot be directly compared with those of all patients at admission to the ward ***(table 4)*** and inferences cannot be made regarding weight changes during the initial treatment. Many patients lost some weight since their admission – mostly due to loss of oedema. By discharge, most had started to gain weight.

Table 6 Details of timing of death: stratified by admission episode; inpatient or outpatient care; HIV status

		Synbiotic	Control	risk ratio *(95% confidence interval)*	p-value
All admissions	TOTAL PATIENT ADMISSION EPISODES	486	467		
	TOTAL DEATHS	108/486 (22.2%)	119/467 (25.5%)	0.87 (0.69 to 1.09)	0.24
	total deaths during inpatient treatment episodes	78/486 (16.1%)	74/467 (15.9%)	1.01 (0.76 to 1.36)	0.93
	HIV +ve inpatient deaths	47/234 (20.1%)	55/246 (22.4%)	0.90 (0.64 to 1.27)	0.54
	HIV -ve inpatient deaths	18/227 (7.9%)	13/207 (6.3%)	1.26 (0.63 to 2.51)	0.51
	total deaths during outpatient treatment episodes	30/394 (7.6%)	45/387 (11.6%)	0.65 (0.42 to 1.02)	0.06
	HIV +ve inpatient deaths	26/186 (14.0%)	31/189 (16.4%)	0.85 (0.53 to 1.38)	0.51
	HIV -ve outpatient deaths	3/202 (1.5%)	11/194 (5.7%)	0.26 (0.07 to 0.92)	0.02
Admission 1	Total 1st admissions	399	396		
	Inpatient deaths total	61/399 (15.3%)	52/396 (13.1%)	1.16 (0.83 to 1.64)	0.38
	HIV +ve inpatient deaths	34/170 (20.0%)	35/192 (18.2%)	1.10 (0.72 to 1.68)	0.67
	HIV -ve inpatient deaths	14/203 (6.9%)	11/190 (5.8%)	1.19 (0.55 to 2.56)	0.65
	Outpatient deaths total	18/324 (5.6%)	39/338 (11.5%)	0.48 (0.28 to 0.82)	0.006
	HIV +ve outpatient deaths	15/134 (11.1%)	25/155 (16.1%)	0.69 (0.38 to 1.26)	0.23
	HIV -ve outpatient deaths	2/182 (0.5%)	11/179 (6.1%)	0.18 (0.04 to 0.80)	0.010
Admission 2	Total 2nd admissions	68	61		
	Inpatient deaths total	12/68 (17.6%)	19/61 (31.1%)	0.57 (0.30 to 1.07)	0.07
	HIV +ve inpatient deaths	9/49 (18.4%)	17/46 (37.0%)	0.50 (0.25 to 1.00)	0.04
	HIV -ve inpatient deaths	3/19 (15.8%)	2/15 (13.3%)	1.18 (0.23 to 6.20)	1.0*
	Outpatient deaths total	11/56 (19.6%)	3/42 (7.1%)	2.75 (0.82 to 9.24)	0.08
	HIV +ve outpatient deaths	10/40 (20.0%)	3/29 (10.3%)	2.42 (0.73 to 8.01)	0.12
	HIV -ve outpatient deaths	1/16 (6.3%)	0/13 (0.0%)	-	1.0*
Admission 3	Total 3rd admissions	16	10		
	Inpatient deaths total	5/16 (31.3%)	3/10 (30.0%)	1.04 (0.32 to 3.44)	1.0*
	HIV +ve inpatient deaths	4/13 (30.8%)	3/8 (37.5%)	0.82 (0.24 to 2.75)	1.0*
	HIV -ve inpatient deaths	1/3 (33.3%)	0/2 (0.0%)	-	1.0*
	Outpatient deaths total	1/11 (0%)	3/7 (42.9%)	0.21 (0.03 to 1.66)	0.24*
	HIV +ve outpatient deaths	1/10 (10.0%)	3/5 (60.0%)	0.17 (0.02 to 1.22)	0.08*
	HIV -ve outpatient deaths	0/2 (0.0%)	0/2 (0.0%)	-	-
Admission 4	Total 4th admissions	3	0		-
	Deaths	0	n/a	-	-

(NB) Note that HIV positive and negatives do not always add up to total because of a small number of unknowns. *Fisher exact

Table 7 Patient characteristics at point of entry to outpatient care (=point of discharge from inpatient care)

	Synbiotic (n=331)	**Control (n=341)**	**relative risk (discrete variables) or *mean difference (continuous variables)* (95% confidence interval)**	**p-value**
1) Demographic profile				
Age in months (mean ± sd)	30.8 ±25.3	28.4 ± 23.2	*2.35 (-1.32 to 6.02)*	0.21
Boys (%)	181/331 (54.7%)	186/341 (54.5%)	0.99 (0.86 to 1.13)	0.86
2) Nutritional Diagnosis *(at admission to ward)*				
Wasting (<70% weight-for-height (NCHS) and/or MUAC <11cm, no oedema)	76/331 (23.0%)	84/341 (24.6%)	0.93 (0.71 to 1.22)	0.61
Kwashiorkor (oedematous malnutrition)	215/331 (65.0%)	201/341 (58.9%)	1.10 (0.98 to 1.24)	0.11
3) Anthropometry (mean Z score ± sd)				
Height-for-Age (HAZ)	-3.13 ± 1.5	-3.09 ± 1.3	*-0.44 (-0.26 to 0.17)*	0.69
Weight-for-Height (WFZ)	-2.24 ± 1.1	-2.44 ± 1.1	*0.20 (0.03 to 0.37)*	0.02
Weight-for-Age (WFZ)	-3.49 ± 1.2	-3.64 ± 1.1	*0.15 (-0.02 to 0.32)*	0.08
4) Child HIV Status (%)				
HIV seropositive	135/331 (40.8%)	157/341 (46.0%)	0.89 (0.74 to 1.05)	0.17
HIV seronegative	186/331 (56.2%)	179/341 (52.5%)	1.07 (0.93 to 1.23)	0.34
Not tested or unknown	10/331 (3.0%)	5/341 (1.5%)	2.06 (0.71 to 5.96)	0.17

NB. This table includes patients successfully discharged from inpatient care (n=324 Synbiotic group, n=338 control)
plus absconders from inpatient care (n=7 Synbiotic group, n=3 control). Absconders are included since they were also followed up in the community to discover final outcome (e.g. whether alive and well when seen at community 'default' visit; whether dead at default visit)

4.3.4 Secondary outcomes – carer reported clinical symptoms

Table 8 shows carer-reported post randomization clinical symptoms. Total days of outpatient observation were less in the Synbiotic group. This was partly because mean time to death was shorter in Synbiotic outpatients who died than in control outpatients who died. Sixteen synbiotic group outpatient deaths contributed a total 617 days of outpatient observation (mean 38.6 days observation per death) whilst 39 control outpatient deaths contributed 1726 days (mean 44.3 days).

Inpatients consuming Synbiotic had more days cough (p=0.05) and vomiting (p=0.05). They also had more days (p=0.01) of severe diarrhoea (≥6 abnormally loose or watery stools). Preceding this increase in severe diarrhoea, non-significant baseline imbalances should be noted (***annex F3***): 73 days/1000 severe inpatient diarrhoea in the Synbiotic group) vs. 65 days/1000 in controls.

Outpatient symptoms were similar between groups. Overall outpatient diarrhoea did not differ, but there was a trend to less severe diarrhoea in the Synbiotic group (p=0.07). Consistent with symptom reports, unscheduled outpatient visits and use of non-routine outpatient medication were similar.

Table 8 Clinical outcomes (carer reported symptoms)

		Synbiotic	Control	p
1) CLINICAL SYMPTOMS ~ total patient days with symptom / 1000 days patient observation				
TOTAL DAYS PATIENT OBSERVATION (median ±IQR)		**12909 (32 ± 25)**	**14124 (33 ± 25)**	**0.04**
TOTAL DAYS INPATIENT OBSERVATION median ±IQR		2517 (5 ± 4)	2525 (6 ± 4)	0.35
TOTAL DAYS OUTPATIENT OBSERVATION, median ± IQR		10408 (32.0 ± 25)	11562 (33 ± 25)	0.03
DIARRHOEA	~ as inpatient	250	202	0.31
	~ severe diarrhoea as inpatient	80	51	0.01
	~ as outpatient	41	41	0.95
	~ severe diarrhoea as outpatient	11	16	0.07
VOMITING	~ as inpatient	273	215	0.05
	~ as outpatient	12	12	0.64
ABDOMINAL PAIN	~ as inpatient	160	166	0.57
	~ as outpatient	19	15	0.43
FEVER	~ as inpatient	310	265	0.21
	~ as outpatient	42	47	0.26
COUGH	~ as inpatient	476	421	0.05
	~ as outpatient	124	106	0.69
FAST / DIFFICULT BREATHING	~ as outpatient	5	7	0.15
2) OUTPATIENT VISITS median ± IQR (total visits)		2 ± 2 (667)	2 ± 2 (702)	0.34
3) USE OF NON-ROUTINE DRUGS ~ prescribed elsewhere since last review ***or*** prescribed at OTP clinic review				
Total visits at which any drugs used / total OTP visits (%)		246/667 (36.9%)	258/702 (36.8%)	0.96
Total visits at which antibiotics used / total OTP visits (%)		151/667 (22.6%)	169/702 (24.1%)	0.53
4) UNSCHEDULED OUTPATIENT CONSULTATIONS (visits/1000 patient days)		9	8	0.93

Table 9 shows indicators of Synbiotic safety: RUTF was tolerated equally well in both groups during inpatient care (p=0.77). During outpatient care, less problems eating RUTF were reported by Synbiotic patients. RUTF (p=0.02). This did not affect the total amount consumed: if RUTF was left unfinished, the amount was small (just over 1 pot unfinished = approx 1 day's ration/14 days) and similar in both groups (p=0.35).

There were no group differences in incidence of sepsis episodes. Similar numbers of patients needed blood cultures (p=0.89) and similar numbers of blood cultures were positive (p=0.28). No cases of probiotic-associated sepsis were detected.

Addressing safety concerns about probiotic use in HIV, **table 9** also shows deaths stratified by HIV serostatus. There was no excess mortality among HIV seropositive Synbiotic patients (p=0.80).

Table 9 Indicators of Synbiotic safety

	Synbiotic	**Control**	**relative risk or** *mean difference (95% confidence interval)*	**p**
1) PROBLEMS WITH RUTF				
AS INPATIENT (patient not tolerating RUTF or clinically worsening ->needing F100 milk instead)	6/396 (1.5%)	5/393 (1.3%)	**1.19 (0.37 to 3.87)**	0.77
AS OUTPATIENT number of visits with problem/total outpatient visits (%)	26/667 (3.9%)	48/702 (6.8%)	**0.57 (0.36 to 0.91)**	0.02
Bottles of RUTF remaining (if ration unfinished), *mean, ± SD*	1.17 ± 2.4	1.35 ± 2.3	*-0.18 (-0.57 to 0.20)*	0.35
2) BLOOD CULTURES & SEPSIS				
Blood culture taken	68/399 (17.0%)	69/396 (17.4%)	**0.98 (0.72 to 1.33)**	0.89
Positive blood culture (of those taken)	17/68 (25.0%)	23/69 (33.3%)	**0.75 (0.44 to 1.27)**	0.28
Probiotic associated blood culture (of those taken)	0 (0%)	0 (0%)	-	-
3) DEATHS ~ by HIV status				
Total HIV seropositive deaths	73/170 (42.9%)	85/192 (44.3%)	**0.97 (0.77 to 1.23)**	0.80
Total HIV seronegative deaths	21/203 (10.3%)	25/190 (13.1%)	**0.79 (0.46 to 1.36)**	0.39
4) TOTAL READMISSION EPISODES*	87/399 (21.8%)	71/396 (17.9%)	**1.22 (0.92 to 1.61)**	0.17
Readmissions who eventually died	29/87 (33.3%)	28/71 (39.4%)	**0.85 (0.56 to 1.28)**	0.43

* Same patient can have more than one readmission episode. Maximum admission episodes was 4.

4.3.5 Kaplan-Meier time-to-death analysis

Figure 11 is a Kaplan-Meier time-to-death graph, split by HIV status, showing all deaths during the course of the study. The adverse effects of HIV manifest quickly in both Synbiotic and control patients. In both HIV positive and negative children there were initially more Synbiotic than control deaths, though as detailed in ***tables 5 and 6***, these early inpatient deaths were statistically not different between groups. Median time to death was 8(± IQR 8) days in Synbiotic patients who died, and 11(± IQR 22) days in controls (p=0.004). A log-rank test for overall time-to-death curves was non-significant (p=0.36). Overall Synbiotic/control differences are non-significant in both HIV classes.

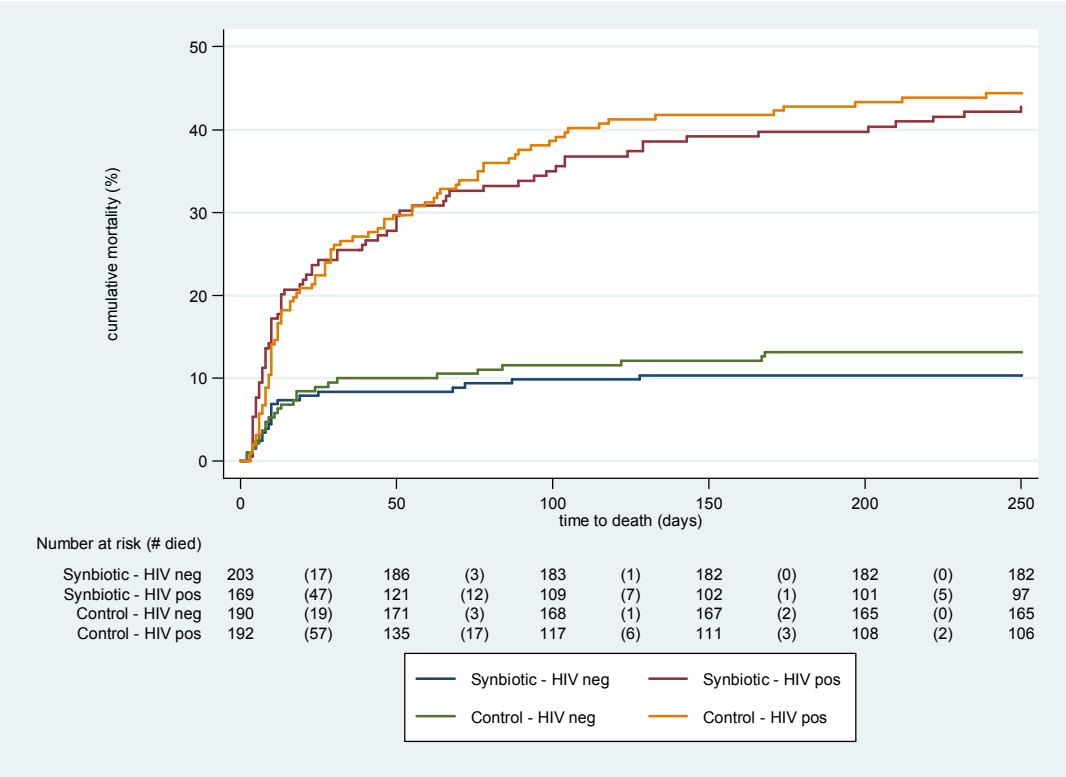


Figure 11 Kaplan-Meier time-to-death graph, by HIV status.
(All deaths in the study are shown)

4.3.6 Subgroup Analyses

Analyses were repeated for the pre-specified subgroup of children who we thought might benefit most from Synbiotic actions: those aged 6 to 60months and without disability or other direct surgical or other cause of SAM. Overall trends and patterns of difference were similar to the whole group. Only main subgroup outcomes are shown in the table below:

Table 10 Main PRONUT study outcomes – main subgroup analysis

	Synbiotic (n=333)	**Control (n=318)**	**relative risk or** *mean difference (95% confidence interval)*	p
PRIMARY OUTCOME:				
1) NUTRITIONAL CURE (total)	189/333 (56.8%)	172/318 (54.1%)	**1.05 (0.91 to 1.23)**	0.49
HIV seropositive cures	58/141 (41.1%)	58/153 (37.9%)	**1.07 (0.84 to 1.36)**	0.57
HIV seronegative cures	127/173 (73.4%)	113/154 (73.4%)	**1.00 (0.79 to 1.26)**	0.99
SECONDARY OUTCOMES:				
2) DEATHS (TOTAL)	85/333 (25.5%)	90/318 (28.3%)	**0.93 (0.78 to 1.11)**	0.42
3) OUTPATIENT DEFAULTERS or WARD ABSCONDERS	23/333 (6.9%)	30/318 (9.4%)	**0.84 (0.61 to 1.15)**	0.24
4) FAILURES OF NUTRITIONAL TREATMENT	11/333 (3.3%)	12/318 (3.8%)	**0.93 (0.60 to 1.44)**	0.75
5) READMISSIONS	20/333 (6.0%)	11/318 (3.5%)	**1.28 (0.97 to 1.68)**	0.13
6) Other: (transfers out; final outcome unknown)	5/333 (1.5%)	3/318 (0.9%)	**1.23 (0.71 to 2.11)**	0.52
7) Rate of weight gain *(mean g/kg/day ± SD)*	4.39 (4.0)	4.14 (4.1)	*0.24 (-0.39 to 0.86)*	0.45
8) Length of stay in programme *(median days to cure ± IQR)*	37 (34 to 48)	38 (34 to 47)		0.66
Outcomes stratified by treatment phase				
~ Deaths (inpatient, during 1st admission)	47/333 (14.1%)	38/318 (11.9%)	**1.09 (0.89 to 1.35)**	0.41
~ Deaths (any time during remainder of study)	38/286 (13.3%)	52/280 (18.6%)	**0.81 (0.63 to 1.05)**	0.09
total deaths during all inpatient treatment episodes (incl. readmissions)	59/397 (14.9%)	56/366 (15.3%)	**0.98 (0.81 to 1.19)**	0.87
total deaths during all outpatient treatment episodes (incl. readmissions)	26/338 (7.7%)	34/310 (11.0%)	**0.82 (0.61 to 1.10)**	0.15
total outpatients deaths following 1st admission only	13/238 (5.5%)	30/280 (10.7%)	**0.65 (0.40 to 1.01)**	0.03

Chapter 5

'FUSAM' study

*(F*ollow-*U*p of long term outcomes from *S*evere *A*cute *M*alnutrition)

5.1 Aims

To describe long term (≥ 1 year post-discharge) mortality and morbidity following an episode of SAM

5.1.1 Objectives:

i. To describe the occurrence and timing of in-programme and post-treatment deaths following an episode of SAM
ii. To describe the extent of catch-up growth in the year following an episode of SAM
iii. To identify risk factors for mortality from SAM:
    a. Risk factors at original admission
    b. Risk factors related to post-SAM care
    c. To determine whether risk factors for short term mortality are similar to those for late deaths

5.2 Methods

5.2.1 Study design

FUSAM was a longitudinal cohort study.

5.2.2 Setting & participants

FUSAM participants were all children cared for on 'MOYO' nutrition ward, Queen Elizabeth Hospital, Blantyre Malawi. All admissions during the period of the PRONUT study from 12th July 2006 to 14th March 2007 were eligible. This spans both the dry (July to December) and rainy, 'hungry' season (December to March). MOYO is profiled in detail in ***chapter 3***.

Those successfully cured in MOYO's OTP programme were asked to return for ward-based review on the 1 year anniversary of their cure date. Non-cures and those failing to return for assessment were followed-up at the home address they had given at original admission.

Where possible and appropriate, information was also collected on siblings of the ex-MOYO patient and the parents or carer of the ex-MOYO patient.

5.2.3 Outcome variables

FUSAM focused on the following:

PRIMARY OUTCOMES

- ***Mortality***

Total mortality consisted of:

  - Short term deaths, whilst still an inpatient on MOYO
  - Medium term deaths, within the 1st 90 days of admission but after the inpatient treatment phase
  - Long term deaths, defined as death >90 days following programme admission.

Short plus medium term deaths approximate 'in-programme' deaths and are considered together in FUSAM analyses whilst long term deaths approximate post-treatment deaths. In reality the division is less distinct since for example: readmissions can be under MOYO care for longer periods; some children may proceed quickly through the treatment programme and be discharged from care, yet still die within 90 days of original admission; some carers abscond not having completed full treatment. The 90 day cut-off was chosen to be consistent with upper limits of time a patient would normally spend in a therapeutic feeding programme: 10 weeks as an outpatient before being defined as 'nutritional failure' plus a preceding 3 weeks of inpatient care.

- ***Long term survival***

Defined as seen alive by the FUSAM study team (or reliably reported to be alive) at ≥1year after the original admission date to MOYO.

SECONDARY OUTCOMES

- ***Anthropometric status at 1 year (catch-up growth):***

To calculate weight-for-height, height-for-age and weight-for-age z-scores, we measured the weight, height, MUAC and exact age of:

- The ex-MOYO child.

  Longitudinal data were thus available at: day of admission to MOYO; day of minimum weight on ward (this was the closest approximation to 'dry'/non-oedamtous weight, though it is important to note that some patients died whilst still oedematous); day of discharge from ward to OTP; each OTP clinic visit (weight and MUAC only); day of OTP exit; day of 1 year follow-up.
- Siblings - defined as children born to the same mother and living in the same family

The following outcomes variables also served as potential explanatory variables in a mathematical model exploring which factors predicted long term survival and mortality:

- . ***Clinical progress in the year since MOYO admission***
  - Recurrence of acute malnutrition
  - Other (non-SAM) health problems resulting in inpatient admission or outpatient visit
  - Clinical symptoms in the previous 2 weeks

  These morbidity questions mirrored what was asked about the 2 weeks prior to original admission to MOYO and at each 2 week interval between OTP visits. In the case of deaths, it also served as a verbal autopsy report.
- ***Access to and use of TFP-related services***
  - For how long, if at all, the child received supplementary feeds following MOYO discharge?
  - Use of TB and HIV-related services, if clinically indicated.
- ***Health education activities and basic nutrition-related knowledge***
  - Did the carer attend any health education sessions whilst on MOYO?
  - Did any differences result from the health education sessions?
  - Did the carer know about basics of nutrition, specifically about Malawi's 'six food groups' (vegetables, fruits, staples, fats, animal foods, legumes & nuts) and about ideal duration of breastfeeding?

5.2.4 Data sources and measurement

Baseline variables

The following groups of independent variables, all potentially affecting FUSAM outcomes, were obtained at original admission to MOYO. Measurement details are described in ***chapter 3***

- Age and anthropometry
- HIV status (including CD4 count, at 1st OTP visit, for HIV seropositive children)
- Clinical status in the 2 weeks prior to ward admission
- Signs and symptoms used for clinical staging of HIV disease (according to 2006 WHO case definitions)[94]
- Past medical history
- Family and socioeconomic status

Sources of baseline variables

Baseline variables were the same as those collected and entered in the PRONUT study database. Whilst a small number of patients declined to be randomized in PRONUT, routine clinical data were available on all patients. Additional data, taken on separate PRONUT forms, were obtained, with permission, from most carers. A key question enabling long term follow-up was the 'verbal map' described in ***chapter 3.5.*** This was critical to both low loss to follow-up in PRONUT, but also laid the ground for the later FUSAM study. All data collection forms, both routine ward forms and PRONUT/FUSAM-specific data collection forms are shown in ***Annexes D and E***.

FUSAM data

FUSAM data collection forms are shown in **Annex G.** A dedicated FUSAM study team of 3 senior nurses participated in piloting of these forms and were trained to use the final versions.

FUSAM reviews were done either at MOYO if a carer returned for a 1 year visit, or at a patient's home if an address was available to trace the patient. Target time for long term follow-up was at least 1 year after original discharge from MOYO treatment.

Some minor differences from PRONUT data collection were:

- ***Measurement of anthropometry.***

In PRONUT, two observers had measured in pairs and were able to repeat any measurements likely to be incorrect: identified by incompatible measurements or implausibly fast growth. In FUSAM field visits logistical constraints (a small field team) meant that the study nurse measured alone, with the trained study driver helping steady and reassure the child. When

measuring siblings, there were no previous measurements to compare against. In such field conditions there was greater potential for error and extreme z-scores were therefore considered more likely to represent measurement errors than a child who is truly very small or very large. Following standard criteria[95], individuals with extreme z-scores were thus excluded from anthropometry-related analysis:

- weight-for-height z-scores, WHZ (NCHS) <-4 or > +6 or
- weight-for-age z-score, WAZ (NCHS) <-6 or >+6 or
- height-for-age z-score HAZ (NCHS) <-6 or >+6

Z-scores were calculated from weight, height/length, age and sex variables using ENA for SMART software, version October 2007[96].

- ***Dates***

In PRONUT, accurate event dates were mostly available since they were observed on the ward. In FUSAM, especially when asking neighbours about date of death, there was on rare occasions some uncertainty. Where the month but not exact date was known, the 15th of the month was taken as the best estimate. If a sibling's age but not year or month of birth was known, then the date was estimated as 1st July of the year which would give the stated age.

5.2.5 Bias

Several factors might have biased results:

- ***Missing data due to logistics constraints***

Completing or fully completing the FUSAM questionnaire was not always possible due to logistical reasons:

- If a home address was not available no visit could be attempted and no information was available on long term outcomes.
- Due to only one field team, one project vehicle and limited project funding, FUSAM visits were only made to children known not to have died before the study started in summer 2007. Some children were known to have died before this time, full FUSAM details were not always known since the full questionnaire had not yet been developed (e.g. asking about compliance with supplementary feeding and HIV treatment services).
- Repeat visits to the same address were rarely made for collecting secondary outcomes alone. (e.g. sibling anthropometry).

- ***Missing data due to patient confidentiality constraints***

In the community setting, it was not always appropriate to ask all the questions covered by the FUSAM questionnaire. e.g. relatives of neighbours sometimes reported that a family had moved

away. In such cases, it was often appropriate to ask whether the ex-MOYO child was alive or dead, but mostly inappropriate to ask further clinical questions.

- **Hawthorne effect**

FUSAM children, whether or not also enrolled in PRONUT, were treated in MOYO during the period of a research study. Though it was primarily a service ward rather than a specialised research unit, the extra staff, inputs and attention to carefully following protocols may have affected treatment impact. This possible effect of this cannot be quantified or adjusted for in analyses and may or may not have implications for generalizability which will be discussed later.

- ***Recall bias***

This might have occurred if carers of children who died systematically recalled details of care and clinical progress differently to those who were still alive at FUSAM visit. For example, carers of children still alive might selectively remember better aspects of their original treatment and forget the worse aspects. The opposite might be true for carers of children who died as they seek to understand and explain the death.

- ***Selection bias due to MOYO admissions system***

MOYO admissions are not representative of all SAM in the community and could even under-represent cases of SAM presenting to the paediatric A&E at Queen Elizabeth Hospital:

- Very sick patients might die in the admissions area or on the special care ward before transfer to MOYO
- Borderline cases might be missed and wrongly sent to the normal paediatric wards instead of to MOYO.

Whilst possible, the potential for these selection biases to influence the overall direction or interpretation of study results is minimal. Firstly, the two biases would likely cancel each other out: the first would cause underestimation of true SAM mortality; the second would underestimate SAM survival since it is the mild, low risk cases who are most likely to be missed.

Furthermore, over the period of this study efforts were made to sensitise all staff in A&E and on the general wards to correctly identify and transfer children with SAM to MOYO. Nursing capacity on MOYO was also good. Patients who in previous years might have been admitted to other wards to receive oxygen or blood or similar were increasingly being looked after on MOYO itself.

Minimising biases

Exploring whether biases might have affected our overall conclusions, I examined baseline characteristics (thus not susceptible to recall bias) of all children. Comparing the profile

of unknowns against those known alive and those known dead gave some indication of what the unknown outcome is more likely to have been.

5.2.6 Study Size

Since baseline data for FUSAM relied on admission information collected by PRONUT, study size was determined by the numbers of children admitted to MOYO during the period of PRONUT enrolment **(*see chapter 4.2.6*).** FUSAM was a follow-on project rather than a completely separate study. Separate a-priori calculations were not therefore done prior to FUSAM.

The strength of any positive findings can be easily seen by confidence intervals. Possible false negative findings can be harder to identify. An advantage of PRONUT in this respect is that it ranks among the larger SAM-related studies. The original sample size of 400 per group was large enough, at 95% significance, 80% power, and accommodating 100 total losses to follow-up, to detect an inter-group difference of 65% vs. 75% cure. To show inter group mortality difference of 25% vs. 15%, 270 patients would be needed per group. Given that 1024 patients were analysed in FUSAM (compared to 796 in PRONUT) it is clear that the effect of most clinically important exposures, even if unevenly distributed, would likely be observed.

5.2.7 Quantitative variables

Time to event in Kaplan-Meier analysis and Cox regression

Beginning time 0 was date of admission to MOYO ward. Small numbers of patients died within hours of admission to the ward. So that they would still be counted in the model, all those who died on day 0 were recoded as 0.5days of FUSAM follow-up. Time to FUSAM follow-up for other patients was calculated in days by subtracting date of admission from date of final known outcome (alive, dead or unknown/other).

Time to follow-up was not constant for all patients, and could be longer for some patients than others because FUSAM visits were organized in batches, according to their home location. Repeat visits were also sometimes necessary to chase missing information, when for example a family was away from home when first visited. With only one follow-up team, it was logistically impossible to visit each patient at a fixed time post admission.

5.2.8 Statistical methods

Data entry and cleaning

Similar to PRONUT, FUSAM data were entered in EpiData 3.1 (EpiData Association, Odense, Denmark, 2003-4). A dedicated data entry file was written with simple macros ('Check' files) that helped ensure high quality data entry, e.g. variables plausible, in-range and consistent with

other related variables. Key data (anthropometry, dates, final outcomes, HIV status) were double entered. This FUSAM database was then merged with the PRONUT database, describing complete patient care from original admission to final outcome.

During data cleaning, inconsistent or unexpected results like long times to final outcome were cross checked against original patient files to ensure no data transcription or entry errors.

Data analysis

Main analyses were performed using Stata Intercooled 10.0™(StataCorp LP, USA).

Chi-square tables and approximate confidence limits for relative risk were used to examine categorical data using StatCalc (CDC, Atlanta, USA, 1993). Where cell numbers are small, Fisher exact results are noted.

To assess the role of HIV as a possible confounder or effect modifier, major analyses included HIV serostatus (positive or negative) as a stratification level.

Wealth index

The PRONUT questionnaire recorded wealth-marking asset ownership (e.g. radio ownership, land ownership, access to electricity, type of water source). These were based on validated questions from the Malawi 2004 Demographic and Health Survey[97]. Principal component analysis[98] was used to convert the multiple wealth items into a single index divided into wealth quintiles.

Kaplan-Meier analysis

Time-to-death 'step-up' curves rather than 'step-down' survival curves are presented, in accordance with suggested best practice[99]. This emphasises mortality as the primary study outcome, and also better demonstrates inter-group differences.

Cox regression

As evident from the initial curves, the effect of HIV appeared to change over time and thus violated the proportional hazards assumption. This was confirmed by a formal test using Schoenfeld residuals. Subsequent analyses are therefore presented stratified by HIV. Other major adjustor variables (admission oedema, admission age, admission MUAC, admission WAZ) did not violate the assumption.

As will be discussed, there is no reason to believe that censored children due to unknown final outcomes had an atypical risk of death compared to non censored children.

Due to tied times to failure especially early on in treatment, the '*exactp*' option within Stata's '*stcox*' command was specified in all reported regression models. This was computationally more complex and hence slower but was the appropriate option in this study given the early tied failures. Using the default option gave minor differences in the detail of the results but no overall important differences which would have led to different conclusions.

5.2.9 Ethics

Following completion of PRONUT, specific permission to follow up children long term was obtained from the COMREC (College of Medicine Research and Ethics Committee). Funding for the study was only obtained in mid 2007, so though the idea had been considered for some time, it was not previously known whether the study would be possible.

Home follow-up is routine in nutrition programmes, follows a previous study based at MOYO[84] and has the particular advantage of being of direct benefit to the patient: being able to identify any problems, advise on, and where necessary refer for further care.

5.3 Results - Study flow chart and summary outcomes

From 12th July 2006 to 14th March 2007, 1024 children were admitted to MOYO. Long term outcome information was found on 899/1024(88%). Short, medium and long term outcomes are summarized in the study flow chart:

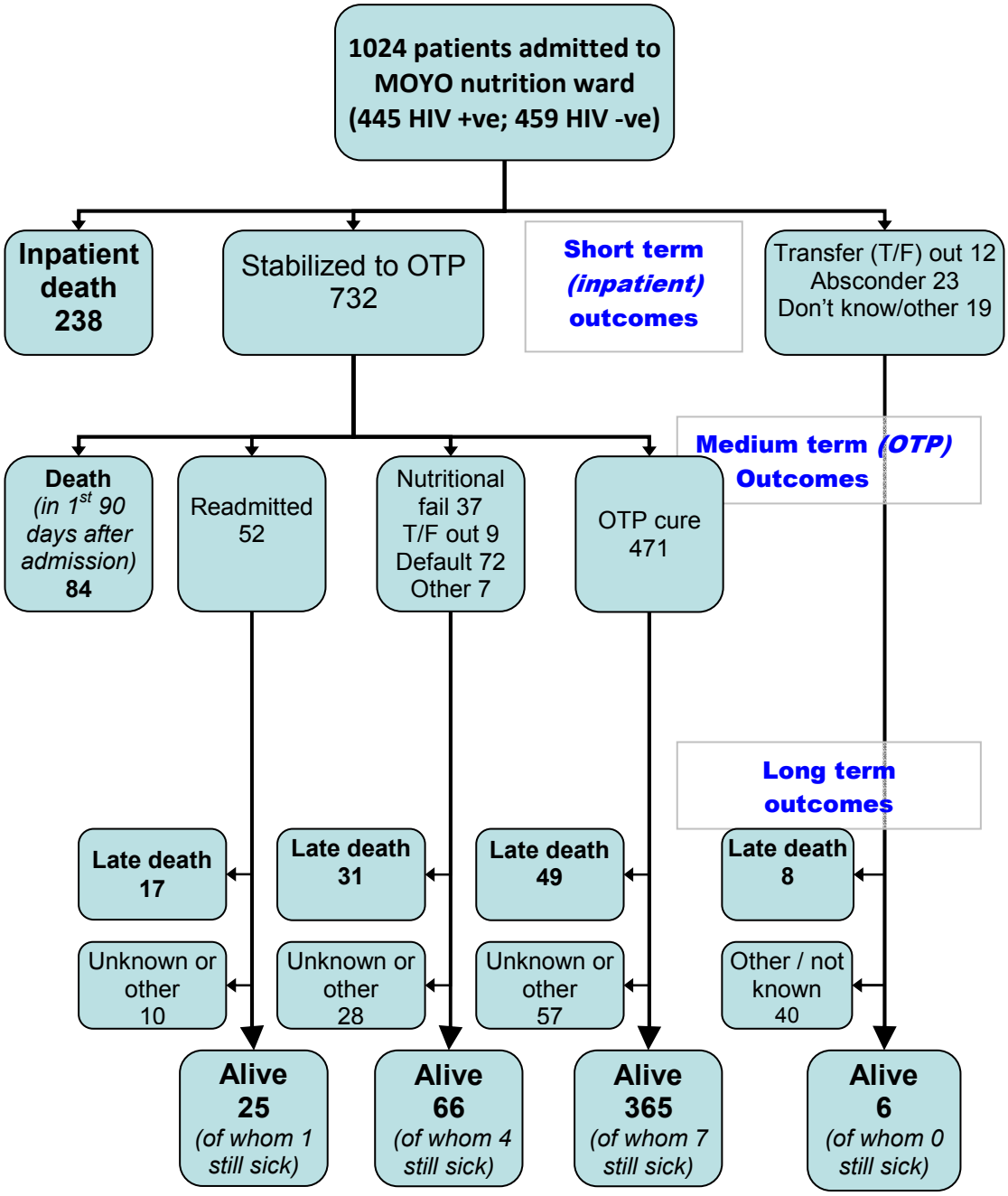


Figure 12 FUSAM study flow chart - all admissions to MOYO

Key long term outcomes are defined as:

- Late death = death ≥90 days after original admission to the ward
- Alive = known alive at ≥ 1year after original admission to the ward.

5.3.1 FUSAM summary - total survivors

A total of 462/1024(45%) children were known to be still alive at a year or more after discharge from treatment. Of these 432/462 (94%) were seen in person by the study team and 30/462 (6%) were reported by family or neighbours to be alive.

Long term survival was greatest amongst children who had been successfully cured following initial treatment. Of 471 discharged from the OTP as nutritionally cured, 365/471 (77%) were still alive at a year or more after their first admission.

5.3.2 FUSAM summary - total mortality

A total of 427/1024 (42%) children were known to have died. As will be explored in subsequent analyses, most deaths were early in the programme:

- 238/427 (56%) children died during initial inpatient treatment
- 84/427 (20%) died in the medium term, within 90 days of programme admission
- 105/427 (25%) died over the longer term follow-up period

Most deaths were in children with underlying HIV:

- 274/427 (64%) of all deaths were known seropositive. Differently expressed, 274/445(62%) of known seropositive children died.
- 77/427 (18%) of all deaths were known seronegative. Differently expressed, 77/459 (17%) of known seronegative children died.
- 76/427 (18%) of all deaths were of unknown status. These were almost all very early ward deaths who died before a test could be done.

5.3.3 FUSAM summary - Total unknown final outcome

Final 1 year status was unknown for 135/1024 (13%) of children originally admitted:

- 45/135 (33%) could not be traced at the address given
- 42/135 (31%) did not give an address in the first place
- 31/135 (23%) had missing notes
- 7/135 (5%) lived too far away for the follow-up team to visit
- 10/135 (7%) were reported alive but at <1year following the original admission. This happened where a family had moved from their original address and relatives or neighbours reported that the child was alive *when last seen*. In such cases, the date of final outcome was the date of that last reliable sighting. No assumptions were made about current status of the child at the 1 year visit.

5.4 Results – Baseline patient profile at admission to MOYO

In this section I present patient characteristics at admission to the MOYO nutrition ward. The results columns highlight key issues which will be explored in subsequent analyses:

- Which admission characteristics are associated with death and which with being still alive ≥1 year later
- Are there any differences between those children who die early (inpatient or OTP deaths) and those who die late (>90 days after admission)
- Do admission characteristics of children whose 1 year outcome is unknown suggest that they are more likely to be dead or alive (i.e. is there a likely systematic bias that would affect the validity of comparing known deaths vs. known live children)

For simplicity, statistical comparisons between the groups are not presented here. Multivariable analyses will be presented later: these are important and necessary to account for issues like weight-based z-score indices in oedematous patients. Because of its known adverse effect on outcomes, relevant results are however stratified by HIV status.

5.4.1 Age & sex profile

Table 11 shows that children who died were younger than those still alive at 1 year. The youngest group were late deaths. The age of those whose final outcome was unknown was more similar to survivors than deaths.

Sex ratio on admission was balanced close to 50% for all outcome groups except late deaths, who have a preponderance of boys.

Table 11 Age and sex of MOYO patients, by final outcome

	All patients ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at ≥1 year post admission (n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Age in months (median, IQR)	**21.5 (15 to 32)**	*19.4 (13 to 30)*	*18.8 (12 to 29)*	*23.3 (17 to 34)*	*23.8 (16 to 36)*
Boys	**543/1024(53%)**	*156/322 (48%)*	*66/105 (63%)*	*251/462 (54%)*	*70/135 (52%)*

5.4.2 Nutritional profile

Table 12 shows that oedematous SAM was the dominant form of malnutrition, accounting for almost 70% of admissions. It was most prevalent among HIV negative patients, 85% of whom had oedematous SAM. Children whose HIV status was unknown had a prevalence of kwashiorkor somewhere between those who were known seropositive and seronegative.

Risk of death was lower in oedematous than in non-oedematous SAM. Whilst severe wasting accounted for 27% of all admissions, it accounted for almost half of all deaths. Most wasted patients had both low weight-for-height and low MUAC. Twelve percent had a low MUAC <11cm alone; one percent had a normal MUAC but low weight-for-height. ***(annex H.1)***

The admission profile of the unknown final outcome group was again more similar to those known alive than those known to have died 1 year.

Table 12 Nutritional diagnosis of MOYO patients at admission, according to final outcome

	All patients ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at ≥1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Kwashiorkor (all)	**697/1024 (68%)**	*175/322 (54%)*	*45/105 (43%)*	*383/462 (83%)*	*94/135 (70%)*
In HIV ⊖	**391/459 (85%)**	*37/57 (65%)*	*13/20 (65%)*	*278/315 (88%)*	*63/67 (94%)*
In HIV ⊕	**237/445 (53%)**	*89/191 (47%)*	*31/83 (37%)*	*98/139 (71%)*	*19/32 (59%)*
In HIV unknown	**69/120 (58%)**	*49/74 (66%)*	*1/2 (50.0%)*	*7/8 (88%)*	*12/36 (33%)*
Severe wasting (all)	**275/1024 (27%)**	*135/322 (42%)*	*55/105 (52%)*	*69/462 (15%)*	*16/135 (12%)*
In HIV ⊖	**61/459 (13%)**	*19/57(33%)*	*7/20 (35%)*	*33/315 (10%)*	*2/67 (3%)*
In HIV ⊕	**184/445 (41%)**	*92/191 (48%)*	*48/83 (58%)*	*32/139 (23%)*	*9/32 (28%)*
In HIV unknown	**30/120 (25%)**	*24/74 (32%)*	*0/2 (0%)*	*1/8 (13%)*	*5/36 (14%)*
Not SAM or unknown	**52/1024 (5%)**	*12/322 (4%)*	*5/105 (5%)*	*10/462 (2%)*	*25/135 (19%)*

5.4.3 Malnutrition severity (weight-for-height, weight-for-age and height-for-age z-scores)

Admission anthropometry is shown in **Table 13**. An expanded version of this table is show in ***annex H.1.2***, where each index is stratified by oedematous and non-oedematous malnutrition, and by HIV status.

The message from this simple version of the results is clear: children who are more malnourished at baseline – whether defined by WHZ, WAZ or HAZ – are more likely to die than those with better z-scores.

Yet again, those with unknown final outcomes have a z-score profile more similar to known survivors than to known deaths.

Table 13 Weight-for-height, weight-for-age and height-for-age mean z-scores at admission, according to final outcome (SD)

	All admissions ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at >1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Weight-for-height	**-2.25 (1.3)**	***-2.77 (1.2)***	***-2.65 (1.2)***	***-1.92 (1.2)***	***-1.86 (1.3)***
Weight-for-age	**-3.59 (1.3)**	***-4.13 (1.1)***	***-4.30 (1.1)***	***-3.18 (1.2)***	***-3.14 (1.4)***
Height-for-age	**-3.23 (1.4)**	***-3.43 (1.4)***	***-3.88 (1.3)***	***-3.03 (1.4)***	***-2.94 (1.5)***
MUAC	**11.6 (2.0)**	***10.6 (1.7)***	***10.6 (1.8)***	***12.3 (1.9)***	***12.2 (2.0)***

5.4.4 HIV related profile

Table 14 shows that HIV was prevalent in the MOYO population. For ease of interpretation, only death and survivor columns are shown: the full version of the table with additional columns for all patients and those with unknown final outcome is in ***annex H.1.3***

HIV status was known for almost 90% of all children. Large numbers of seronegative children also had symptoms and signs which would traditionally be considered as HIV staging criteria. Common reasons for them to have a stage 3 or 4 diagnosis include previous admissions to SFP, TFP and oral candida.

Clinical staging in both HIV seropositive and seronegative patients was more advanced among patients who died than in those alive at 1 year. CD4 was also lower among deaths, whether expressed as mean of all values or as % of children below the age-adjusted 'severely low' threshold.

Table 14 Baseline HIV profile, according to final outcome

	Inpatient or OTP death (n=322)	*Late death* (n=105)	**Alive at >1 year post admission (n=462)**
Child HIV status			
HIV ⊖	*57 (18%)*	*20 (19%)*	*315 (68%)*
HIV ⊕	*191 (59%)*	*83 (70%)*	*139 (30%)*
HIV unknown	*74 (23%)*	*2 (2%)*	*8 (2%)*
HIV staging: *HIV ⊖* ***only***	*n=52*	*n=20*	*n=307*
Stage 0	*7 (14%)*	*3 (15%)*	*86 (28%)*
Stage 1 or 2	*6 (12%)*	*5 (25%)*	*51 (17%)*
Stage 3	*35 (67%)*	*8 (40%)*	*129 (42%)*
Stage 4	*4 (8%)*	*4 (20%)*	*41 (13%)*
HIV staging: *HIV ⊕* ***only***	*n=185*	*n=83*	*n=134*
Stage 0	*14 (8%)*	*9 (11%)*	*19 (14%)*
Stage 1 or 2	*21 (11%)*	*6 (7%)*	*26 (19%)*
Stage 3	*101 (55%)*	*53 (64%)*	*65 (49%)*
Stage 4	*49 (27%)*	*15 (18%)*	*25 (18%)*
CD4*	*n=31*	*n=63*	*n=93*
CD4 severely low (age adjusted %)†	*27 (87%)*	*40 (63%)*	*45 (48%)*
CD4%, mean (SD)	*12.9 (8.4)*	*17.1 (8.2)*	*20.5 (10.6)*

* Taken for HIV positive patients only, mostly taken at 1st outpatient visit, 2 weeks after discharge from ward. Small numbers also available for ward patients.
†Age adjusted thresholds for low CD4 were: CD4 <25% for infants aged <12 months; <20% for those aged 12 to 35 months; <15% for those aged 36 to 59months; <15% for those aged 60 months or older *(Source: ARV therapy of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach (2006 revision) World Health Organization)*

5.4.5 Clinical profile

Table 15 shows the clinical profile of children at admission. For simplicity, only death and alive at 1 year columns are presented, with the full version of the table in ***Annex H.1.4***.

Several issues are important to note:

- Almost all children present with symptoms of illness other than malnutrition. These were severe enough to have justified, for most children, visits to OTP clinics or taking of medication in the two weeks prior to MOYO admission.
- Symptom prevalence was highest in children who died as inpatients or during OTP. For some but not all symptoms it was lowest in the 1 year survivors.
- Common use of traditional charms (commonly necklaces, bracelets and string waist bands) may indicate prevalent beliefs in and use of traditional medicines prior to seeking MOYO care.
- Prevalence of breastfeeding until 2 years was low, and lowest among those who died.
- Clinically obvious disability was not uncommon and mostly comprised neurodisability such as cerebral palsy. Disability was commonest amongst those children who died.

Table 15 Baseline clinical profile, according to final outcome

	Inpatient or OTP death (n=322)	*Late death (n=105)*	**Alive at >1 year post admission (n=462)**
Symptoms in previous 2 weeks			
Any	*309/311 (99%)*	*102/105 (97%)*	**447/460 (97%)**
Fever	*205/311 (66%)*	*73/104 (70%)*	**293/458 (64%)**
Diarrhoea	*231/310 (75%)*	*72/105 (69%)*	**280/456 (61%)**
Vomiting	*163/313 (52%)*	*42/105 (40%)*	**203/458 (44%)**
Abdominal pain	*123/269 (46%)*	*37/104 (36%)*	**188/452 (42%)**
Fast or difficult breathing	*45/303 (15%)*	*20/104 (19%)*	**62/457 (14%)**
Cough	*193/308 (63%)*	*76/105 (72%)*	**254/459 (55%)**
Anorexia	*169/294 (57%)*	*51/104 (49%)*	**230/454 (51%)**
Flaky paint dermatosis	*49/306 (16%)*	*14/104 (13%)*	**89/452 (20%)**
Other	*84/314 (27%)*	*34/104 (33%)*	**101/454 (22%)**
Outpatient consultations in 2 weeks prior to admission (any)			
Any	*204/271 (75%)*	*68/102 (67%)*	**318/456 (70%)**
Medication use in last 2 weeks prior to admission			
Any	*264/296 (89%)*	*95/103 (92%)*	**394/450 (88%)**
Anaemia			
Any (PCV<30)	*103/294 (35%)*	*39/96 (41%)*	**141/424 (33%)**
Severe (PCV <15)	*11/294 (4%)*	*1/96 (1%)*	**5/424 (1%)**
Malaria *(+ve thick blood film)*	*9/292 (3%)*	*3/94 (3%)*	**21/415 (5%)**
Has traditional medicine amulet or charm	*87/266 (32%)*	*25/100 (25%)*	**108/444 (24%)**
Breastfed (<2 year olds only)	*102/192 (53%)*	*47/69 (68%)*	**79/243 (33%)**
Disability (any)	*24/282 (9%)*	*9/102 (9%)*	**22/453 (5%)**

5.4.6 Past medical history

Table 16 shows past medical history. Again only three columns are shown for simplicity, the full table is in ***Annex H.1.5***.

High morbidity is experienced by all children. Many have had recent inpatient admissions or admissions for previous SAM. Almost all had outpatient episodes in the last 6 months. Almost one quarter of those with outpatient visits reported signs of symptoms consistent with SAM – yet were not then referred for inpatient treatment which at the time was standard treatment (CTC was not then available in Blantyre district).

Table 16 Past medical history

	Inpatient or OTP death (n=322)	*Late death* (n=105)	**Alive at >1 year post admission (n=462)**
Past inpatient and outpatient episodes (any)			
Inpatient admissions *(non-SAM, in past year)*	*88/283 (31%)*	*22/102 (22%)*	**69/444 (16%)**
Inpatient admissions *(for SAM, ever)*	*47/282 (17%)*	*15/102 (15%)*	**57/452 (13%)**
Outpatient episodes *(last 6 months)*	*233/253 (92%)*	*90/98 (92%)*	**396/440 (90%)**
Outpatient episodes *(last 6 months, **with symptoms suggestive of malnutrition**)*	*60/254 (24%)*	*26/97 (27%)*	**84/437 (19%)**
Outpatient episodes *(for SFP, ever)*	*62/267 (23%)*	*29/102 (28%)*	**93/445 (21%)**
Ex Low Birth weight (reported by carer)	*29/257 (11%)*	*13/98 (13%)*	**39/449 (9%)**
Ever had TB	*15/273 (5%)*	*4/103 (4%)*	**10/450 (2%)**
Ever had measles vaccine	*232/290 (80%)*	*81/98 (82%)*	**401/448 (90%)**

5.4.7 Family and socioeconomic status

Table 17 shows the family profile (full table in ***annex H.1.6***). Key results include:

- There is a high prevalence of orphaning:

- Almost a quarter of families have lost a previous child

- There was no obvious pattern in birth order of the MOYO child

- Most mothers reported having had at least primary school education, yet almost a third also described themselves as illiterate.

- Fathers were overall better educated than mothers, with fewer reports of illiteracy.

Table 17 Family profile

	Inpatient or OTP death	*Late death*	**Alive at >1 year post admission**
	(n=322)	*(n=105)*	**(n=462)**
Orphan			
Mother died	*18/264 (7%)*	*10/102 (10%)*	**36/457 (8%)**
Father died	*22/261 (8%)*	*9/102 (9%)*	**28/452 (6%)**
Both dead	*9/240 (4%)*	*4/91 (4%)*	**10/410 (2%)**
Previous child death in family	*76/306 (25%)*	*24/103 (23%)*	**110/457 (24%)**
Birth order of MOYO child			
First	*76/272 (28%)*	*26/103 (25%)*	**126/453 (28%)**
Second	*70/272 (26%)*	*26/103 (25%)*	**115/453 (25%)**
Third	*60/272 (22%)*	*20/103 (19%)*	**87/453 (19%)**
Fourth or later	*66/272 (24%)*	*31/103 (30%)*	**125/453 (28%)**
Maternal education			
None	*30/254 (12%)*	*13/98 (13%)*	**51/433 (12%)**
Primary school	*164/254 (65%)*	*70/98 (71%)*	**303/433 (70%)**
Secondary school	*60/254 (24%)*	*15/98 (15%)*	**79/433 (18%)**
Paternal education			
None	*10/176 (6%)*	*1/68 (1%)*	**14/337 (4%)**
Primary school	*77/176 (44%)*	*31/68 (46%)*	**156/337 (46%)**
Secondary school	*89/176 (51%)*	*36/68 (53%)*	**167/337 (50%)**
Mother illiterate	*88/256 (34%)*	*35/100 (35%)*	**160/437 (37%)**
Father illiterate	*25/233 (11%)*	*5/93 (5%)*	**36/423 (9%)**

Table 18 shows socioeconomic status (and ***annex H.1.7*** the full version of this table).

Three results are noteworthy:

- Over half of all children arrive to MOYO having been referred from their local health centre. (NB This should *not* count as visit to outpatient clinic in the last two weeks, though I cannot exclude the possibility that some patients misinterpreted the question)

- Children from richer families appear to be at greater risk of death than those from poorer families.

- Most families have access to piped or borehole water which is generally good drinking quality.

Table 18 Socioeconomic status & residence

	Inpatient or OTP death *(n=322)*	*Late death* *(n=105)*	**Alive at >1 year post admission** **(n=462)**
Mother's occupation			
Housewife	*135/322 (42%)*	*55/105 (52%)*	**242/462 (52%)**
*Ganyu**	*44/322 (14%)*	*16/105 (15%)*	**81/462 (18%)**
Employee/ self employed	*63/322 (20%)*	*25/105 (24%)*	**95/462 (21%)**
Other or unknown	*80/322 (25%)*	*9/105 (9%)*	**44/462 (10%)**
Father's occupation			
Unemployed	*76/322 (24%)*	*17/105 (16%)*	**66/462 (14%)**
*Ganyu**	*38/322 (12%)*	*17/105 (16%)*	**86/462 (19%)**
Employee/self employed/other or unknown	*208/322 (65%)*	*71/105 (68%)*	**310/462 (67%)**
Rural residence	*82/256 (32%)*	*34/99 (34%)*	**191/451 (42%)**
Admitted to MOYO:			
Direct to MOYO or readmission	*90/244 (37%)*	*35/98 (36%)*	**124/427 (29%)**
Via other QECH paediatric ward	*22/244 (9%)*	*10/98 (10%)*	**21/427 (5%)**
Referred from other clinic	*132/244 (54%)*	*53/98 (54%)*	**282/427 (66%)**
Wealth quintile			
Poorest	*43/240 (18%)*	*17/95(18%)*	**97/426 (23%)**
2nd poorest	*49/240 (20%)*	*14/95 (15%)*	**92/426 (22%)**
Middle	*44/240 (18%)*	*23/95 (24%)*	**82/426 (19%)**
2nd richest	*50/240 (21%)*	*15/95 (16%)*	**83/426 (19%)**
Richest	*54/240 (23%)*	*26/95 (27%)*	**72/426 (17%)**
Main household water source			
Piped	156/264 (59%)	59/101 (58%)	**227/455 (50%)**
Borehole	74/264 (28%)	29/101 (29%)	**177/455 (39%)**
Well or spring	34/264 (13%)	13/101 (13%)	**51/455 (11%)**
Main household toilet			
Flush toilet	5/264 (2%)	4/101 (4%)	**12/455 (3%)**
Traditional pit (own)	110/264 (42%)	30/101 (30%)	**179/455 (39%)**
Traditional pit (shared)	148/264 (56%)	67/101 (66%)	**259/455 (57%)**
Bush toilet or other	1/264 (0.4%)	0/101 (0%)	**5/455 (1%)**

*Ganyu is short term seasonal labour such as clearing overgrown roadside grass after the rainy season, in return for cash or in-kind payment.

5.5 What explains mortality or survival? Kaplan-Meier failure curves and Cox regression

5.5.1 Kaplan-Meier failure curve – all patients

A total of 1003 children were included in this analysis. Of the 21/1024(2.1%) of original admissions not included, date of final outcome was unknown for 1 child who died and for 20 whose long term outcome was unknown.

Mean follow-up time was 278 days (SD 249), range 0.5 days to 809 days. Median time to final *long-term* outcome was 287 days, IQR 11 to 529.

The unadjusted curve in ***figure 13*** confirms a key message already noted in the study flow chart: most mortality occurs soon after admission to programme. Median time to death was 10 days, IQR 3 days to 69 days. This compares to median time in programme (defined as from admission to final *programme* outcome e.g. time-to-cure; time to failure of nutritional therapy) of 33 days, IQR 9 to 43 days.

278/427 (65%) of deaths occurred within 30 days of admission. The 1 year Kaplan-Meier mortality rate was 42% (95%CI 39% to 45%) and the 2 year mortality rate was 48% (95% CI 44% to 52%).

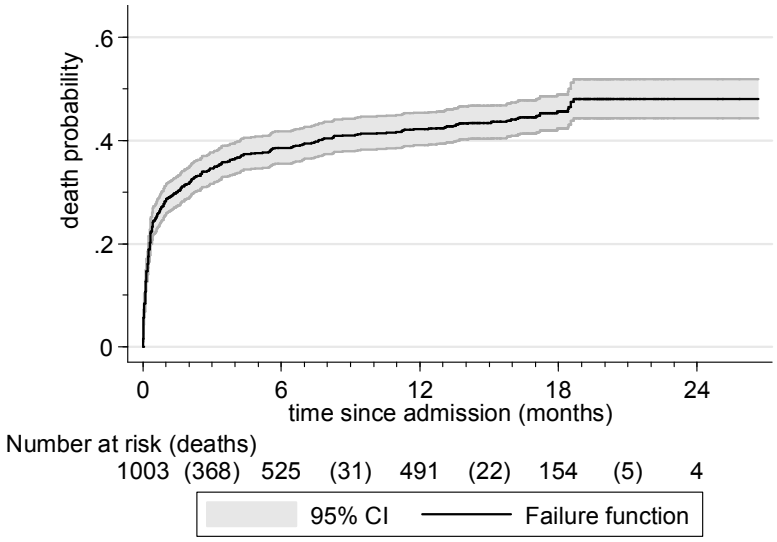


Figure 13 Kaplan Meier failure curve, all patients in the study.

The table below the graph shows:

- numbers of children 'at risk' at the beginning of a particular time period (e.g. 1003 children are in the study at time=0; 525 remain under follow-up at 6 months.)
- (in parentheses), deaths in a given time period (e.g. 368 children died between 0 and 6 months; 31 died between 6 and 12 months)

The number at risk in a particular time period is not simply the number previously at-risk minus the number died. Other outcomes are also possible (e.g. default; moved away). These children also drop out of the analysis (are 'censored'): hence the denominator changes and the y-axis is mortality *probability* rather than percentage.

5.5.2 Kaplan-Meier failure curves – by HIV

Failure curves by HIV serostatus illustrate the marked adverse impact of HIV on mortality.

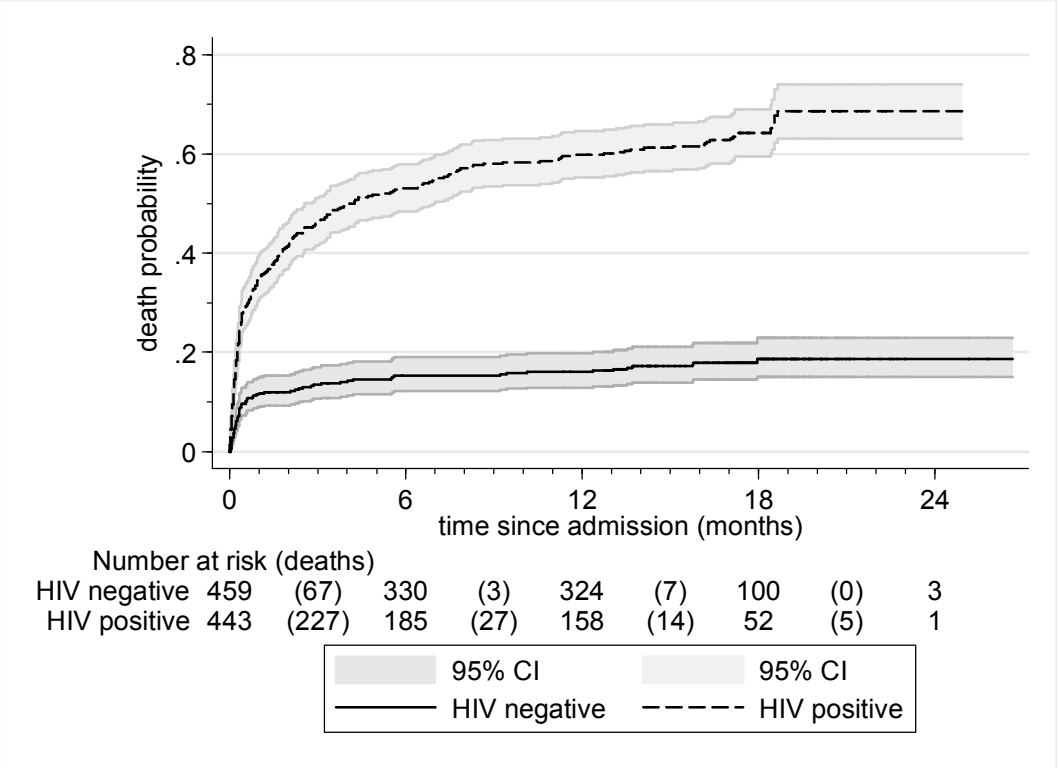


Figure 14 Kaplan Meier failure curves, by HIV serostatus

For both HIV negative and positive patients, most deaths occur soon after admission. For HIV negative patients, ongoing mortality after the first 90 days does occur but is limited. This contrasts with HIV positive patients who experience high rates of ongoing mortality, even later than 1 year post-admission (table 19). HIV related risks are not thus constant over the whole time period, which is why most of the reported Cox regression tables are presented stratified by HIV. The Log-rank test for difference between HIV negative and positive mortality was $p<0.0001$.

Table 19 Kaplan-Meier failure function showing early mortality probability at 30 and 90 days, and late mortality probability at 1 and 2 years after admission to programme

	Time after admission to programme			
	30 days	90 days	1 year	2 years
HIV negative (n=459)	12% (9 to 15)	13% (11 to 17)	16% (13 to 20)	19% (15 to 23)
HIV positive (n=445)	35% (30 to 39)	46% (42 to 51)	60% (55 to 65)	69% (63 to 74)

5.5.3 What explains adverse SAM outcomes – malnutrition severity?

Severity of malnutrition at admission to a therapeutic feeding programme is known to strongly predict short term mortality. ***Table 20*** shows that it also predicts total (short, mid and long term combined) mortality in the FUSAM study. Adjusting for age, oedema and HIV, low baseline MUAC <11cm, WHZ <-3 and WAZ <3 are all strongly associated with death, whereas low HAZ is not. The effect of age is inconsistent, with under 12month olds alone having significantly elevated hazards for mortality. There is no clear age-related hazard gradient.

Table 20 Cox regression exploring baseline anthropometry as a predictor of death at 2 years

Risk factor		Number of deaths	% dead by 2 year	Hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)	P (adj.)
Sex	Girls	202/469 (43%)	48 (43 to 54)	Ref.	Ref.	
	Boys	221/530 (42%)	48 (43 to 53)	0.92 (0.76 to 1.12)	1.00 (0.81 to 1.24)	0.97
Age group (in months)	>= 60m	30/88 (34%)	37 (28 to 49)	1.11 (0.58 to 2.12)	1.14 (0.55 to 2.37)	0.72
	48 to <60m	13/42 (31%)	33 (21 to 51)	Ref.	Ref.	
	36 to <48m	25/68 (37%)	40 (29 to 54)†	1.27 (0.65 to 2.49)	1.69 (0.80 to 3.55)	0.17
	24 to <36m	85/230 (37%)	37 (31 to 44)†	1.26 (0.70 to 2.25)	1.19 (0.61 to 2.32)	0.61
	12 to <24m	176/430 (41%)	47 (41 to 53)	1.42 (0.81 to 2.49)	1.45 (0.76 to 2.78)	0.26
	0 to <12m	97/145 (67%)	67 (59 to 75)	2.89 (1.62 to 5.17)	2.30 (1.17 to 4.51)	0.02
Oedema	No	205/305 (67%)	74 (68 to 80)	Ref.	Ref.	
	Yes	220/694 (32%)	35 (31 to 40)	0.37 (0.30 to 0.44)	0.56 (0.44 to 0.71)	<0.001
MUAC	≥ 11cm	152/563 (27%)	30 (26 to 34)	Ref.	Ref.	
	< 11cm	266/428 (62%)	69 (64 to 75)	2.94 (2.40 to 3.60)	1.71 (1.29 to 2.28)	<0.001
WHZ	≥ -3	217/674 (32%)	38 (33 to 43)	Ref.	Ref.	
	< -3	189/295 (64%)	69 (63 to 75)	2.62 (2.15 to 3.20)	1.81 (1.42 to 2.31)	<0.001
WAZ	≥ -3	57/314 (18%)	22 (17 to 29)	Ref.	Ref.	
	< -3	365/681 (54%)	59 (55 to 64)	3.71 (2.80 to 4.91)	2.23 (1.58 to 3.13)	<0.001
HAZ	≥ -3	132/415 (32%)	35 (30 to 41)	Ref.	Ref.	
	< -3	282/570 (49%)	56 (51 to 61)	1.71 (1.39 to 2.11)	1.21 (0.95 to 1.55)	0.13
HIV	Negative	77/459 (17%)	19 (15 to 23)	Ref.	Ref.	
	Positive	**273/443 (62%)**	**69 (63 to 74)**	**4.93 (3.82 to 6.36)**	**4.06 (3.10 to 5.30)**	**<0.001**

* Adjusted for age, oedema, and HIV

Table 21 shows the same risk factors expressed as continuous rather than categorical variables. Due to the non-proportionality of risks, HIV negative and positive children are shown separately. Adjusted for admission oedema and age, higher admission WHZ, WAZ and MUAC and oedema are all associated with decreased risk of death. The hazard ratios represent the reduction in risk for each unit increase in z-score or cm of MUAC. As with the previous analysis, low HAZ is not associated with increased mortality. For HIV negative children, the magnitude of risk reduction per unit improved WHZ, WAZ and MUAC is similar for both short and long term mortality. For HIV positive patients, adjusted WHZ and MUAC are not associated with short term mortality risk but are highly associated with long term risk. WAZ is related to both, but more strongly to long term outcomes than short term outcomes, as evidenced by the lower hazard ratio of 0.76 vs 0.85.

Table 21 Cox regression exploring baseline anthropometry as a risk factor for death in 1st 90 days vs. all deaths, by HIV serostatus (adjusted hazard ratios)

Risk factor		Hazard ratio for death in 1st 90 days*				Hazard ratio for all deaths (short, mid and long term)*			
		HIV negative	p	HIV positive	p	HIV negative	p	HIV positive	p
Sex	Boys	0.93 (0.54 to 1.60)	0.80	0.95 (0.71 to 1.28)	0.75	1.12 (0.71 to 1.76)	0.63	0.95 (0.74 to 1.21)	0.69
Age	>= 60m	0.60 (0.06 to 6.10)	0.67	0.51 (0.18 to 1.46)	0.21	0.80 (0.20 to 3.32)	0.75	1.31 (0.56 to 3.10)	0.54
	48 to <60m	Ref.	-	Ref.	-	Ref.	-	Ref.	-
	36 to <48m	0.82 (0.09 to 7.78)	0.87	0.49 (0.17 to 1.44)	0.20	0.79 (0.18 to 3.56)	0.76	2.17 (0.91 to 5.17)	0.82
	24 to <36m	0.86 (0.11 to 7.04)	0.89	0.51 (0.19 to 1.36)	0.18	0.60 (0.16 to 2.18)	0.44	1.45 (0.66 to 3.21)	0.35
	12 to <24m	1.81 (0.24 to 13.68)	0.57	0.48 (0.18 to 1.26)	0.14	0.92 (0.28 to 3.00)	0.88	1.77 (0.82 to 3.84)	0.15
	0 to <12m	1.78 (0.22 to 14.30)	0.59	0.53 (0.19 to 1.44)	0.21	1.68 (0.48 to 5.86)	0.41	2.57 (1.15 to 5.75)	0.02
Oedema present		0.33 (0.17 to 0.63)	0.001	0.89 (0.65 to 1.22)	0.49	0.35 (0.21 to 0.58)	<0.001	0.63 (0.48 to 0.81)	<0.001
Admission WHZ†		0.72 (0.56 to 0.93)	0.01	0.89 (0.76 to 1.03)	0.13	0.72 (0.57 to 0.90)	0.004	0.77 (0.68 to 0.88)	<0.001
Admission WAZ†		0.66 (0.51 to 0.86)	0.002	0.85 (0.73 to 1.00)	0.05	0.66 (0.53 to 0.82)	<0.001	0.76 (0.66 to 0.87)	<0.001
Admission HAZ†		0.85 (0.71 to 1.02)	0.10	0.93 (0.83 to 1.05)	0.25	0.85 (0.72 to 1.00)	0.06	0.95 (0.86 to 1.05)	0.33
Admission MUAC†		0.77 (0.65 to 0.93)	0.005	0.92 (0.83 to 1.03)	0.15	0.77 (0.65 to 0.90)	0.001	0.83 (0.76 to 0.91)	<0.001

† Hazard ratios represent hazard of death for each unit increase. e.g. for 1 z-score increase in admission WHZ, the hazard ratio for death in 1st 90 days for HIV negative patients is 0.72 (0.56 to 0.93), (="the risk of death significantly decrease as WHZ improves").

Table 22 explores how discharge anthropometry, adjusted for admission status affects mortality risk. Only those children whose initial OTP outcome was cure are analysed in this table. This is to avoid autocorrelation: were deaths included, that would be misleading, since anthropometry at death for those who die soon after admission is very close to anthropometry at admission and anthropometry at admission has already been shown to predict death. So the purpose of this table is to add some temporal 'gap' and discriminate between those who have a better and worse *discharge* anthropometry whilst controlling for how they were at admission.

The table shows that a better weight gain (in g/kg/day) is associated with significantly less deaths, but in HIV positive patients only. It also shows that higher discharge MUAC is associated with significantly less death, but in HIV negative patients only. For every 1cm better MUAC at discharge (adjusted for admission MUAC, oedema, sex, age and admission WAZ), the hazards of death is reduced by 0.41 (95% CI 0.19 to 0.91). Though not significant, there is also a trend towards the same finding in HIV positive children (p=0.13).

Table 22 Cox regression exploring discharge anthropometry as a risk factor for death, by HIV serostatus

Risk factor	Hazard ratio for all deaths (short, mid and long term)*			
	HIV negative	p	HIV positive	p
Discharge WHZ	0.83 (0.36 to 1.91)	0.67	0.74 (0.41 to 1.32)	0.30
WHZ change (z-scores)	0.56 (0.25 to 1.28)	0.17	0.65 (0.40 to 1.07)	0.09
Weight gain (g/kg/day)	1.01 (0.81 to 1.27)	0.92	0.87 (0.77 to 0.99)	0.03
Discharge WAZ	0.63 (0.20 to 2.00)	0.44	0.68 (0.35 to 1.32)	0.26
WAZ change (z-scores)	0.63 (0.20 to 2.00)	0.44	0.68 (0.35 to 1.32)	0.26
Discharge MUAC (cm)	0.41 (0.19 to 0.91)	0.03	0.73 (0.49 to 1.09)	0.13
MUAC change (cm)	0.59 (0.26 to 1.32)	0.20	0.73 (0.48 to 1.10)	0.13

* Adjusted for *admission* oedema, age, and sex, WAZ and MUAC

5.5.4 What explains adverse SAM outcomes – HIV status?

Hazard ratios in ***table 23*** and subsequent tables are adjusted for sex and age as well as admission oedema and WAZ. This is because they may plausibly affect clinical, family and socioeconomic variables. For example, carers may selectively prioritize older children or male children when seeking medical care. Hence even though not associated with mortality on univariate analyses, age and sex are kept in the model. Only MUAC rather than MUAC *and* WHZ is included because both are markers of wasting and hence highly correlated with each other. WAZ meanwhile represents another facet of nutritional status and is included. HAZ is not included since on univariable analysis (***table 20***) it is not shown to predict mortality.

The strong adverse impact of HIV seropositivity has already been noted in Kaplan-Meier failure curves in ***section 5.5.2***. ***Table 23*** addresses the hypothesis that more advanced disease, assessed by WHO clinical staging criteria for HIV severity, is associated with worse outcomes. As noted in ***section 5.4.4***, both HIV positive *and* HIV negative malnourished children have signs and symptoms consistent with WHO criteria that are usually applied only to HIV positive children. Both are therefore presented.

Table 23 shows that severity of illness at admission, expressed by WHO clinical stage, is not related to ether short or long term mortality risk. Severely low CD4 does however predict mortality. The hazard ratio is highest for short term mortality though wide confidence intervals mean it is not statistically significant. Severely low CD4 (which, is in effect, terminal AIDS) is a highly significant predictor of long term mortality, though the hazard ratio is just 1.89 (1.18 to 3.03).

Table 23 Cox regression exploring signs and symptoms of HIV disease a risk factor for death in 1st 90 days vs. all deaths, by HIV serostatus

Risk factor	Hazard ratio for death in 1st 90 days*				Hazard ratio for all deaths (short, mid and long term)*			
	HIV negative	p	HIV positive	p	HIV negative	p	HIV positive	p
HIV stage 0	Ref.	-	Ref.	-	Ref.	-	Ref.	-
Stage 1 or 2	0.60 (0.16 to 2.30)	0.46	1.11 (0.55 to 2.24)	0.77	1.80 (0.76 to 4.28)	0.19	0.81 (0.46 to 1.43)	0.46
Stage 3	1.47 (0.60 to 3.64)	0.40	0.88 (0.50 to 1.57)	0.67	1.88 (0.92 to 3.83)	0.08	1.14 (0.72 to 1.79)	0.58
Stage 4	0.63 (0.16 to 2.45)	0.51	0.86 (0.46 to 1.63)	0.65	1.22 (0.45 to 3.30)	0.69	1.28 (0.76 to 2.14)	0.35
Severe low CD4 (age-adjusted)	n/a	-	3.24 (0.92 to 11.4)	0.07	n/a	-	1.89 (1.18 to 3.03)	0.008

* Adjusted for admission oedema, age, sex, WAZ and MUAC. NB. Stage 0 represents no signs and symptoms of HIV. Stage 4 represents advanced disease.

5.5.5 What explains adverse SAM outcomes – baseline clinical severity of illness?

Table 24 explores clinical factors predicting short and long term mortality. Of symptoms in the previous 2 weeks, diarrhoea in HIV negative patients is associated with increased hazards of short term mortality. Fast or difficult breathing is associated with short term death in HIV negative patients and long term deaths in HIV positive patients. In both cases however, the hazards are reduced rather than increased, as might be clinically more plausible. This highlights the risk of multiple analyses: chance alone may yield statistically significant findings which are not necessarily indicative of real processes or risks.

Other statistically significant findings which are more plausibly real are

- Increased mortality hazards for severe anaemia in HIV negative patients in the short term and for HIV positive patients in the long term.
- Increased mortality hazards for not breastfeeding in HIV negative children for short term mortality alone
- Increased mortality hazards associated with disability. The hazard is elevated for all groups, though wide confidence intervals mean it is only significant for short term HIV positive deaths and long term HIV negative deaths.

Table 24 Cox regression exploring clinical status at admission as a risk factor for death in 1st 90 days vs all deaths, by HIV serostatus

Risk factor	Hazard ratio for death in 1st 90 days*				Hazard ratio for all deaths (short, mid and long term)*			
	HIV negative	p	HIV positive	p	HIV negative	p	HIV positive	p
Symptoms in previous 2 weeks								
Fever	0.66 (0.35 to 1.25)	0.20	0.97 (0.70 to 1.34)	0.84	0.96 (0.58 to 1.58)	0.87	0.85 (0.65 to 1.12)	0.25
Diarrhoea	2.04 (1.05 to 3.97)	0.04	0.81 (0.57 to 1.14)	0.23	1.59 (0.95 to 2.68)	0.08	1.15 (0.88 to 1.51)	0.31
Vomiting	1.71 (0.91 to 3.22)	0.10	1.20 (0.88 to 1.62)	0.25	0.84 (0.52 to 1.37)	0.49	1.23 (0.96 to 1.58)	0.10
Abdominal pain	1.38 (0.72 to 2.63)	0.33	1.28 (0.92 to 1.78)	0.14	1.41 (0.86 to 2.30)	0.17	0.99 (0.76 to 1.28)	0.92
Fast or difficult breathing	0.32 (0.14 to 0.77)	0.01	0.82 (0.54 to 1.25)	0.36	1.12 (0.59 to 2.12)	0.72	0.71 (0.51 to 0.99)	0.04
Cough	0.93 (0.49 to 1.76)	0.83	1.03 (0.75 to 1.42)	0.19	1.06 (0.65 to 1.74)	0.80	1.03 (0.79 to 1.36)	0.80
Anorexia	1.15 (0.58 to 2.28)	0.68	1.21 (0.87 to 1.66)	0.26	0.75 (0.46 to 1.22)	0.25	1.17 (0.91 to 1.51)	0.22
Flaky paint dematosis	1.00 (0.52 to 1.94)	0.99	0.99 (0.60 to 1.67)	0.99	1.66 (0.93 to 2.96)	0.09	1.14 (0.75 to 1.72)	0.54
Other	0.95 (0.49 to 1.83)	0.87	0.91 (0.65 to 1.26)	0.57	1.10 (0.65 to 1.87)	0.72	1.04 (0.80 to 1.35)	0.78
Outpatient visits (any)	1.65 (0.76 to 3.58)	0.21	1.14 (0.79 to 1.63)	0.49	1.29 (0.75 to 2.20)	0.36	1.03 (0.77 to 1.38)	0.83
Any drugs	1.08 (0.42 to 2.77)	0.88	1.19 (0.68 to 2.11)	0.54	0.80 (0.42 to 1.52)	0.49	1.11 (0.67 to 1.83)	0.69
Anaemia								
Any (PCV<30)	0.90 (0.47 to 1.74)	0.76	0.92 (0.66 to 1.28)	0.61	1.08 (0.65 to 1.80)	0.76	1.05 (0.80 to 1.36)	0.73
Severe (PCV <10)	11.95 (1.66 to 86.19)	0.01	1.38 (0.59 to 3.23)	0.45	2.19 (0.66 to 7.23)	0.20	2.62 (1.18 to 5.84)	0.02
Malaria	0.28 (0.04 to 2.18)	0.22	0.93 (0.36 to 2.38)	0.88	0.26 (0.04 to 1.88)	0.18	0.94 to 0.46 to 1.95)	0.88
Has traditional medicine amulet or charm	1.25 (0.67 to 2.32)	0.48	0.98 (0.67 to 1.42)	0.90	1.40 (0.81 to 2.40)	0.23	1.00 (0.73 to 1.35)	0.99
Not breastfed (<2 year olds only)	3.06 (1.34 to 6.95)	0.01	1.36 (0.80 to 1.35)	0.13	0.67 (0.36 to 1.26)	0.21	0.98 (0.70 to 1.38)	0.92
Disability (any)	1.97 (0.82 to 4.69)	0.13	2.37 (1.11 to 5.07)	0.03	2.77 (1.43 to 5.34)	0.002	1.76 (0.94 to 3.28)	0.08

* Adjusted for oedema, age, sex , admission WAZ and admission MUAC

5.5.6 What explains adverse SAM outcomes – risk factors in past medical history?

Table 25 explores features of a child's past medical history as a risk factor for death. Differences by HIV serostatus are evidenced by differing hazard ratios, though few are statistically significant. Ever having had TB is the only factor which significantly increases the hazards of mortality: then only in HIV positive patients and only for short term deaths alone. The magnitude of this effect is not great: 2.20 (1.18 to 4.10) increased hazards.

Table 25 Cox regression exploring past medical history as a risk factor for death in 1st 90 days vs all deaths, by HIV serostatus

Risk factor	Hazard ratio for death in 1st 90 days*				Hazard ratio for all deaths (short, mid and long term)*			
	HIV negative	p	HIV positive	p	HIV negative	p	HIV positive	p
Past inpatient and outpatient episodes (any)								
Inpatient admissions *(non-SAM, in past year)*	0.78 (0.34 to 1.77)	0.54	1.46 (1.03 to 2.05)	0.03	1.03 (0.55 to 1.91)	0.94	1.31 (0.99 to 1.75)	0.06
Inpatient admissions *(for SAM, ever)*	0.65 (0.14 to 3.08)	0.58	0.84 (0.59 to 1.28)	0.42	0.49 (0.18 to 1.35)	0.17	1.22 (0.86 to 1.75)	0.27
Outpatient episodes *(last 6 months)*	1.60 (0.49 to 5.21)	0.44	1.10 (0.58 to 2.09)	0.76	0.69 (0.34 to 1.40)	0.30	0.69 (0.40 to 1.21)	0.20
Outpatient episodes *(last 6 months, **with symptoms suggestive of malnutrition**)*	1.89 (0.82 to 4.34)	0.14	0.75 (0.52 to 1.09)	0.13	1.33 (0.74 to 2.41)	0.34	1.00 (0.74 to 1.36)	1.00
Outpatient episodes *(for SFP, ever)*	1.30 (0.62 to 2.72)	0.49	0.72 (0.49 to 1.06)	0.10	0.72 (0.40 to 1.32)	0.29	0.92 (0.69 to 1.23)	0.58
Ex Low Birth weight *(reported by carer)*	1.99 (0.79 to 4.98)	0.15	1.17 (0.70 to 1.96)	0.55	1.39 (0.69 to 2.81)	0.36	0.74 (0.49 to 1.12)	0.16
Ever had TB	4.85 (0.50 to 47.11)	0.17	2.20 (1.18 to 4.10)	0.01	2.81 (0.35 to 22.7)	0.33	1.27 (0.77 to 2.09)	0.35
Ever had measles vaccine	1.59 (070 to 3.63)	0.27	0.70 (0.40 to 1.20)	0.19	1.60 (0.71 to 3.58)	0.26	0.96 (0.61 to 1.50)	0.85

* Adjusted for oedema, age, sex, admission WAZ and admission MUAC

5.5.7 What explains adverse SAM outcomes – family and socioeconomic risk factors?

Table 26 shows that adjusted for age, sex and admission oedema, WAZ and MUAC, and most types of orphaning have no significant effect on mortality. There is a possible trend to effect in HIV negative double orphans (p=0.07). Parental education or literacy likewise have no clear effect on mortality. Birth order is statistically relevant, but only for short term mortality: hazards are increased for third-born HIV positive children and for fourth-born (or later) HIV negative children (though the wide confidence intervals likely reflect small numbers). Hazards are lowest for children who were second-born.

Table 27 explores socioeconomic risk factors for mortality. Parental occupation does not appear to have a role, and neither does rural residence, water source, or socioeconomic quintile. There is no clear socioeconomic risk gradient: essential background for interpreting the sole elevated hazard of short term death in 2nd richest HIV positive patients.

Admission route to MOYO also does not appear to affect mortality risk. There is a non-significant trend towards increased hazards of short term death for those admitted first to another of the Queen's hospital paediatric wards and only then to MOYO. This is plausible given that most such admissions were very sick children admitted to the "Special Care ward" on account of better overnight nursing numbers in the high dependency unit.

Table 26 Cox regression exploring family risk factors for death in 1st 90 days vs all deaths, by HIV serostatus

Risk factor	Hazard ratio for death in 1st 90 days*				Hazard ratio for all deaths (short, mid and long term)*			
	HIV negative	p	HIV positive	p	HIV negative	p	HIV positive	p
Orphan								
Mother died	1.48 (0.32 to 6.82)	0.62	1.24 (0.66 to 2.33)	0.50	0.97 (0.35 to 2.70)	0.95	0.72 (0.45 to 1.15)	0.17
Father died	1.88 (0.52 to 6.87)	0.34	1.10 (0.62 to 1.93)	0.75	1.33 (0.52 to 3.42)	0.56	1.35 (0.84 to 2.16)	0.21
Both dead	2.18 (0.43 to 10.94)	0.35	1.27 (0.46 to 3.48)	0.65	2.78 (0.92 to 8.34)	0.07	1.07 (0.47 to 2.45)	0.17
Previous child death in family	0.59 (0.24 to 1.48)	0.27	1.04 (0.73 to 1.47)	0.84	0.54 (0.26 to 1.14)	0.11	0.89 (0.67 to 1.18)	0.42
Birth order of MOYO child								
First	1.43 (0.63 to 3.24)	0.39	1.88 (1.22 to 2.91)	0.005	1.05 (0.55 to 2.02)	0.88	0.95 (0.66 to 1.36)	0.77
Second	Ref	-	Ref.		Ref.		Ref.	
Third	1.11 (0.38 to 3.26)	0.85	1.57 (1.01 to 2.42)	0.04	0.78 (0.35 to 1.74)	0.55	1.03 (0.72 to 1.47)	0.87
Fourth or later	8.16 (3.06 to 21.71)	<0.001	1.66 (1.06 to 2.61)	0.03	0.97 (0.48 to 1.93)	0.92	0.83 (0.58 to 1.18)	0.29
Maternal education								
None	Ref.		Ref.		Ref.		Ref.	
Primary school	1.05 (0.41 to 2.63)	0.93	0.74 (0.42 to 1.30)	0.29	1.06 (0.53 to 2.13)	0.87	0.78 (0.51 to 1.20)	0.27
Secondary school	0.47 (0.13 to 1.76)	0.26	0.84 (0.46 to 1.53)	0.57	0.57 (0.21 to 1.54)	0.27	0.97 (0.60 to 1.57)	0.91
Paternal education								
None	Ref.		Ref.		Ref.		Ref.	
Primary school	1.53 (0.17 to 13.47)	0.70	1.26 (0.51 to 3.12)	0.61	2.84 (0.38 to 21.26)	0.31	0.89 (0.39 to 2.04)	0.79
Secondary school	0.76 (0.08 to 6.93)	0.81	1.28 (0.53 to 3.08)	0.58	2.31 (0.30 to 17.53)	0.42	0.80 (0.35 to 1.84)	0.60
Mother illiterate	1.24 (0.66 to 2.34)	0.51	1.01 (0.70 to 1.48)	0.94	1.16 (0.71 to 1.91)	0.54	0.97 (0.73 to 1.30)	0.85
Father illiterate	1.12 (0.39 to 3.24)	0.21	1.11 (0.61 to 2.05)	0.73	1.05 (0.44 to 2.48)	0.91	0.85 (0.50 to 1.45)	0.56

* Adjusted for oedema, age, sex and admission WAZ and admission MUAC

Table 27 Cox regression exploring socioeconomic risk factors for death in 1st 90 days vs all deaths, by HIV serostatus

Risk factor	Hazard ratio for death in 1st 90 days*				Hazard ratio for all deaths (short, mid and long term)*			
	HIV negative	p	HIV positive	p	HIV negative	p	HIV positive	p
Mother's occupation								
Housewife	Ref.		Ref.		Ref.		Ref.	
Ganyu	1.37 (0.62 to 3.01)	0.43	1.27 (0.79 to 2.05)	0.33	1.13 (0.62 to 2.05)	0.70	1.03 (0.70 to 1.52)	0.88
Employee/ self employed	1.08 (0.48 to 2.45)	0.86	1.07 (0.73 to 1.57)	0.72	1.45 (0.78 to 2.72)	0.24	0.95 (0.70 to 1.29)	0.74
Other or unknown	1.22 (0.56 to 2.68)	0.61	1.38 (0.91 to 2.11)	0.13	2.51 (1.27 to 4.95)	0.008	1.08 (0.76 to 1.54)	0.65
Father's occupation								
Unemployed	Ref.		Ref.		Ref.		Ref.	
Ganyu	1.09 (0.40 to 2.96)	0.86	0.77 (0.43 to 1.36)	0.37	0.75 (0.35 to 1.62)	0.47	0.81 (0.51 to 1.30)	0.39
Employee/self employed/other or unknown	1.08 (0.50 to 2.33)	0.84	0.85 (0.57 to 1.27)	0.44	0.83 (0.44 to 1.58)	0.58	1.00 (0.72 to 1.38)	0.98
Rural residence	0.97 (0.49 to 1.94)	0.94	0.80 (0.56 to 1.15)	0.22	0.67 (0.39 to 1.13)	0.13	0.82 (0.62 to 1.10)	0.62
Admitted to MOYO:								
Direct to MOYO or readmission	Ref.		Ref.		Ref.		Ref.	
Via other QECH paediatric ward	2.77 (0.90 to 8.54)	0.08	1.74 (0.95 to 3.21)	0.07	1.56 (0.60 to 4.07)	0.37	0.90 (0.56 to 1.43)	0.65
Referred from other clinic	0.89 (0.39 to 2.00)	0.77	1.00 (0.69 to 1.46)	0.99	0.68 (0.39 to 1.18)	0.18	0.86 (0.65 to 1.14)	0.29
Wealth quintile								
Poorest	Ref.		Ref.		Ref.		Ref.	
2nd poorest	1.32 (0.42 to 4.20)	0.64	1.17 (0.63 to 2.14)	0.62	1.35 (0.63 to 2.89)	0.43	0.67 (0.41 to 1.09)	0.10
Middle	0.72 (0.24 to 2.18)	0.56	1.15 (0.67 to 1.98)	0.61	1.11 (0.50 to 2.44)	0.80	0.95 (0.61 to 1.47)	0.82
2nd richest	1.16 (0.37 to 3.61)	0.80	2.08 (1.19 to 3.65)	0.01	1.49 (0.69 to 3.26)	0.31	0.93 (0.59 to 1.45)	0.75
Richest	0.72 (0.17 to 3.11)	0.66	1.16 (0.70 to 1.94)	0.56	0.95 (0.38 to 2.42)	0.92	0.91 (0.60 to 1.38)	0.66
Main household water source								
Piped	Ref.		Ref.		Ref.		Ref.	
Borehole	1.08 (0.54 to 2.16)	0.83	0.85 (0.59 to 1.24)	0.40	0.72 (0.42 to 1.23)	0.23	0.90 (0.67 to 1.21)	0.50
Well or spring	1.08 (0.46 to 2.55)	0.86	0.92 (0.54 to 1.59)	0.77	1.09 (0.51 to 2.32)	0.83	0.90 (0.60 to 1.37)	0.63

* Adjusted for oedema, age, sex, admission WAZ and admission MUAC

5.6 Results - Profile of children found at long term FUSAM follow-up

This section profiles the children found by the FUSAM follow-up team. A total of 667/1024 (65%) original admissions were eligible for a visit. The other 357/1024 (35%) were already known to have died: 322/1024 (31%) as inpatients or during the first 90 days of outpatient treatment; a further 35 (3%) after 90 days of original admission, most often following a readmission episode).

Of the 667 eligible for FUSAM follow-up ***(figure 15):*** 436/667 (65%) were seen in person by the FUSAM study team; 107/667 (16%) were reported on by relatives or neighbours; 44/667 (7%) could not be found at the address given; 42/667 (6%) did not give an address in the first place; 31/667 (5%) had missing notes so could not be traced; 7/667 (1%) lived too far away to make a visit possible.

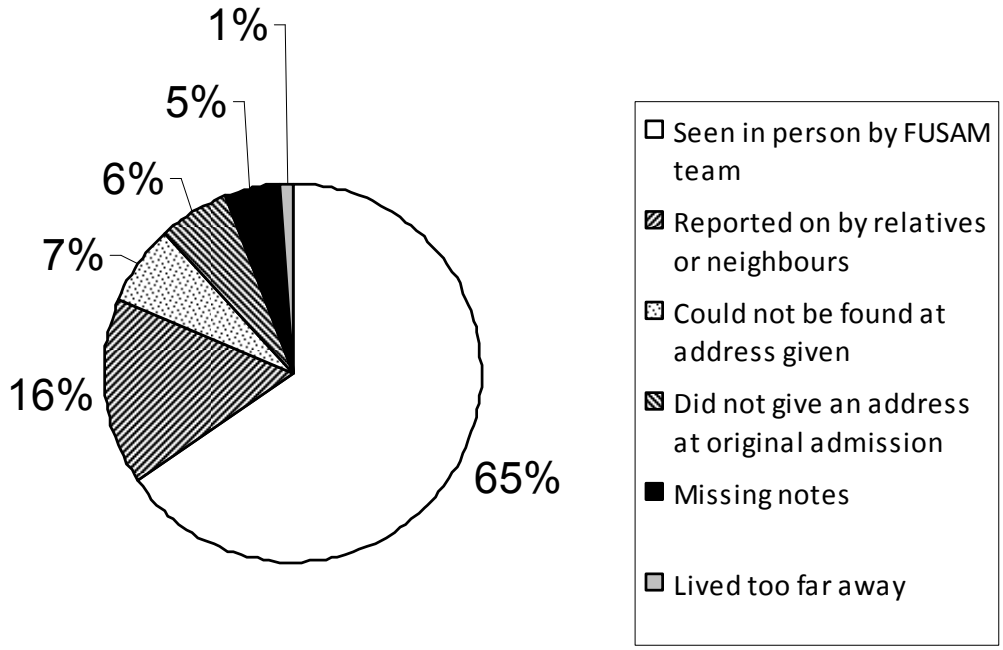


Figure 15 Outcome of FUSAM visit (n=667 patients eligible for visit)

Children found at FUSAM visit to be late deaths were compared against those found to be still alive. Characteristics of HIV positives children and HIV negative children were also compared. So that the latter comparison was not confounded by higher HIV-related mortality, HIV positive children still alive were compared with HIV negative children still alive.

It is important to note minor differences in the denominators in the tables: this reflects missing information where for example a close relative who was not the primary carer (e.g. father or grandmother) was answering but did not know details about a treatment, or where it was inappropriate to ask a neighbour about HIV related issues.

5.6.1 Recurrence of malnutrition

Table 28 shows recurrence of malnutrition reported by carers at FUSAM visit. Recurrence of both oedematous and non-oedematous malnutrition was significantly higher in children who were found to have died. Recurrence of non-oedematous malnutrition was also higher in HIV positive children still alive long term compared to HIV negatives still alive.

At original admission, oedematous malnutrition represented almost 70% of all SAM. In contrast, recurrences of SAM comprised similar numbers of oedematous and non-oedematous episodes (13% and 9% overall).

If SAM did recur, it mostly resulted in readmission to inpatient care. Small numbers of recurrences were treated as outpatients: CMAM services were just starting up in Blantyre district towards the end of the study period. SAM recurrences in HIV negative patients were less likely to be admitted than recurrences in HIV positive children.

Table 28 Recurrence of malnutrition in children followed up at long term FUSAM visit: by mortality and by HIV status

	All FUSAM patients	*by long term (≥90day) mortality (as determined at FUSAM visit)*			***by HIV status (children ALIVE at FUSAM visit only)***		
		Late death	Alive at > 1year	P†	HIV positive	HIV negative	P†
	(n=543)	(n=64)	(n=462)		(n=139)	(n=315)	
Malnutrition Recurrence (any)	**107/512 (21%)**	28/56 (50%)	77/446 (17%)	<0.001	30/133 (23%)	44/305 (14%)	0.04
Oedematous	**65/510 (13%)**	16/55 (29%)	48/445 (11%)	<0.001	15/133 (11%)	31/304 (10%)	0.73
Non-oedematous	**44/509 (9%)**	13/54 (24%)	30/445 (7%)	<0.001	16/132 (12%)	13/305 (4%)	0.002
Admission for inpatient care (if SAM)	**82/97 (85%)**	21/23 (91%)	59/72 (82%)	0.35‡	27/29 (93%)	30/41 (73%)	0.03

† Chi^2 test. ‡Fisher exact results where expected cell value is less than 5

5.6.2 Clinical progress since discharge

Table 29 summarises clinical progress since discharge from MOYO treatment. Compared to children found alive at FUSAM, those who died had similar numbers of outpatient visits in the preceding 6 months but significantly more inpatient admissions. These did not include admissions or visits immediately before death. Of the 64 late deaths identified at FUSAM, 32/64 (50%) reported dying at home and 21/64 (33%) reported dying in hospital.

Incidence of all symptoms asked about was significantly greater in the 2 weeks prior to death than in the 2 weeks prior to FUSAM visit for those found still alive. Exact causes of death could not be determined, but the incidence rate ratio (IRR) was highest for fast breathing (IRR 31.8, 95% CI 19.7 to 53.2) suggesting respiratory disease as the main cause of mortality.

Of patients found alive at FUSAM, HIV positive patients were significantly more likely than HIV negatives to have been admitted for inpatient care in the past year. They were also more likely to have had an outpatient consultation in the last 6 months. Except for cough and fast breathing symptoms in the past two weeks were similar in HIV positive and negative patients.

Table 29 Inpatient admissions, outpatient visits and clinical symptoms at long term FUSAM visit: by mortality and by HIV status

	All FUSAM patients	*by long term (>90day) mortality (as determined at FUSAM visit)*			***by HIV status (children ALIVE at FUSAM visit only)***		
	(n=543)	Late death (n=64)	Alive at >1year (n=462)	P†	HIV positive (n=139)	HIV negative (n=315)	P†
Any inpatient admissions in last 12 months (non-SAM)	**88/517 (17%)**	15/50 (30%)	72/456 (16%)	0.01	35/137 (26%)	34/311 (11%)	<0.001
Any outpatient visits in last 6 months (non-SAM)	**190/496 (38%)**	22/44 (50%)	166/446 (37%)	0.10	60/134 (45%)	104/306 (34%)	0.03
Any clinical symptoms in last 2 weeks	**186/501 (37%)**	43/46 (93%)	139/442 (31%)	<0.001	42/131 (32%)	97/306 (32%)	0.94
Symptoms in last 2 weeks (total patient days with symptom standardized to per 1000 days observation)							
Total days of observation	**7014**	*644*	*6286*		*1904*	*4298*	
Fever	**67**	144	60	<0.001	56	63	0.31
Diarrhoea	**32**	130	23	<0.001	25	22	0.53
Vomiting	**17**	60	12	<0.001	14	12	0.45
Fast breathing	**14**	12	4	<0.001	8	2	<0.001
Cough	**45**	135	35	<0.001	61	25	<0.001
Oedema	**14**	98	5	<0.001	6	5	0.64
Other	24	65	19	<0.001	17	20	0.34

† Chi2 test.

5.6.3 Access to supplementary feeding following discharge

Upon discharge from MOYO therapeutic feeding, all children are referred for four months supplementary feeding (SFP). ***Table 30*** shows that most children received some SFP but only about half got the full four months recommended. Receipt of SFP was not associated with reduced long term mortality. It was also similar amongst HIV positive and negative patients.

Most carers (232/450, 52%) reported no problems with the SFP service. The commonest reported problem was food being out of stock (57/450, 13%). Next most common were problems with SFP staff: being rude or unhelpful for example (41/450, 9%). The least common problems are grouped together as 'other'. They included a sick or depressed carer; the child being temporarily looked after by somebody other than the carer; the carer being advised by friends or relatives not to do and the child being well, so that SFP was perceived as not needed.

Table 30 Access and duration of supplementary feeding post discharge from TFP

	All FUSAM patients	*by long term (>90day) mortality (as determined at FUSAM visit)*			***by HIV status (children ALIVE at FUSAM visit only)***		
		Late death	Alive at 1yr	P†	HIV positive	HIV negative	P†
	(n=543)	(n=64)	(n=462)		(n=139)	(n=315)	
Had SFP (any)	**391/489**	39/49	349/434	0.89	102/125	242/302	0.73
	(80%)	(80%)	(80%)		(82%)	(80%)	
Had ≥4 months SFP	**239/489**	23/49	215/434	0.73	71/125	142/302	0.07
	(49%)	(47%)	(50%)		(57%)	(47%)	

† Chi2 test.

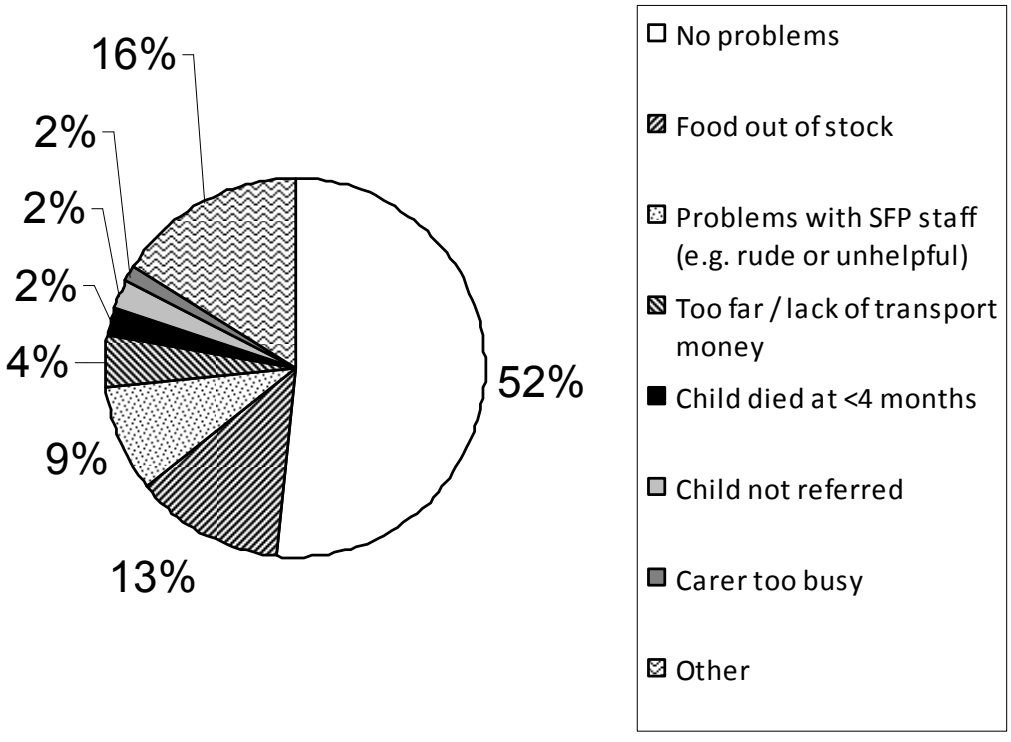


Figure 16 Carer reported problems with SFP (n=450)

5.6.4 Access to TB services

Of 543 patients reviewed at FUSAM visit, 39/494 (8%) answering the question about TB reported ever having treatment. ***Table 31*** shows details of TB treatment and explores differences amongst: those found dead and those found alive at FUSAM; HIV positive and negative children found alive at FUSAM. It shows that TB was significantly more prevalent among children who died and among HIV positive children. In these cases TB most likely reflects high risk patients. Most cases were diagnosed while the child was still under MOYO TFP care (where children were investigated on the basis of clinical suspicion e.g. due to a positive family history; chronic cough; non-response or poor response to other treatments). Small numbers do not allow easy evaluation of the effect of TB treatment. Most children received the recommended treatment period of ≥6 months. Those having less than 6 months treatment were more likely to be late deaths (p=0.04): this may just reflect high risk patients who died *within* 6 months of start of treatment rather than being *because* they didn't complete treatment. Problems and reasons for not completing full treatment include: unhelpful TB clinic staff; the child dying whilst still on treatment. Contact screening and treatment of other children in the family was poor: only 6/39 (15%) carers reported this had been done.

Table 31 TB treatment described at long term follow-up visit

	All FUSAM patients	*by long term (>90day) mortality (as determined at FUSAM visit)*			***by HIV status (children ALIVE at FUSAM visit only)***		
	(n=543)	Late death (n=64)	Alive at 1yr (n=462)	P†‡	HIV positive (n=139)	HIV negative (n=315)	P†‡
Ever had TB treatment	**39/494 (8%)**	12/46 (26%)	27/439 (6%)	<0.001	16/133 (12%)	10/299 (3%)	<0.001
IF TB:							
Started pre-MOYO	**8/39 (21%)**	3/12 (25%)	5/27 (19%)	0.68	4/16 (25%)	1/10 (10%)	0.62
Started whilst on MOYO ward / OTP	**25/39 (64%)**	7/12 (58%)	18/27 (67%)	0.72	11/16 (69%)	7/10 (70%)	1
Started post-MOYO	**6/39 (15%)**	2/12 (17%)	4/27 (15%)	1	1/16 (6%)	2/10 (20%)	0.54
If TB: had ≥6 months treatment	**29/39 (74%)**	6/12 (50%)	23/27 (85%)	0.04	13/16 (81%)	9/10 (90%)	1
If TB: Were other children screened or treated	**6/39 (15%)**	0/12 (0%)	6/27 (22%)	0.15	3/16 (19%)	3/10 (30%)	0.64
If TB: No problems reported with the treatment	**24/39 (62%)**	5/12 (42%)	19/27 (70%)	0.15	13/16 (81%)	6/10 (60%)	0.37

† Chi2 test. ‡Fisher exact results where expected cell value is less than 5

5.6.5 Access to HIV services

Of 543 patients seen at FUSAM visits, 195 were already known HIV seropositive from their time in programme. ***Table 32*** describes their treatment, focusing on use of ARV medication and cotrimoxazole prophylaxis.

A total of 89/159 (56%) children reported having started ARVs. Numbers on ARVs were 20% higher among those still alive than those who died, though this difference was just short of statistical significance at 0.05 level. Baseline HIV clinical staging was however similar. The effect of ARV start time could not easily be compared due to small numbers, but it is notable that few patients who died had started ARVs prior to MOYO.

ARV compliance was good among those reporting: 69/71 (97%) reported last taking ARVs 'today' (or on the day of death if died) and 69/71 (97%) reported last missing a dose more than a month ago (or more than a month prior to death).

Table 32 HIV related services: antiretrovirals (ARVs) and cotrimoxazole prophylaxis

	All HIV positive FUSAM patients	*by long term (>90day) mortality (as determined at FUSAM visit)*		
		Late death	Alive at 1yr	P†‡
	(n=195)	(n=48)	(n=139)	
On ARVs	**89/159 (56%)**	15/35 (42%)	74/122 (61%)	0.06
If on ARVs:				
Started pre-MOYO	**17/89 (19%)**	1/15 (7%)	16/74 (22%)	0.29
Started on MOYO (ward or OTP)	**28/89 (31%)**	8/15 (53%)	20/74 (27%)	0.05
Started after MOYO	**44/89 (49%)**	6/15 (40%)	38/74 (51%)	0.42
Not on ARVs because assessed not to be eligible yet	**14/159 (9%)**	2/35 (6%)	12/122 (10%)	0.74
On cotrimoxazole	**149/161 (93%)**	33/36 (92%)	115/123 (93%)	0.71
If on cotrimoxazole:				
Started pre-MOYO	**21/149 (14%)**	3/33 (9%)	18/115 (16%)	0.41
Started on MOYO (ward or OTP)	**121/149 (81%)**	30/33 (91%)	90/115 (78%)	0.10
Started after MOYO	**7/149 (5%)**	0/33 (0%)	7/115 (6%)	0.35
If on cotrimoxazole:				
Last took dose today or yesterday	**95/149 (64%)**	14/18 (78%)	81/115 (70%)	0.52
Last took dose more than a month ago or never since OTP	**33/149 (22%)**	3/18 (17%)	28/115 (24%)	0.56
HIV clinical staging (as recorded at original admission)				
0	**28/190 (15%)**	5/48 (10%)	19/134 (14%)	0.51
1 or 2	**31/190 (16%)**	5/48 (10%)	26/134 (19%)	0.23
3	**99/190 (52%)**	30/48 (63%)	65/134 (49%)	0.10
4	**32/190 (17%)**	8/48 (17%)	24/134 (18%)	0.85
Severely low CD4 (age adjusted)	**70/135 (52%)**	22/38 (58%)	45/93 (48%)	0.32

† Chi2 test. ‡Fisher exact results where expected cell value is less than 5

The striking feature of ***table 33*** is that a large proportion of mothers reported having had an HIV test, with many of those being tested on MOYO (along with their child – family testing and counselling was always offered alongside testing for the index child). In contrast, less than 50% of fathers had been tested. Siblings were even less likely to have been tested. (***table 34***)

Table 33 Parental HIV status & treatment described at long term follow-up visit

	All FUSAM patients	*by long term (>90day) mortality (as determined at FUSAM visit) (HIV positive children only)*			***by long term (>90day) mortality (as determined at FUSAM visit) (HIV negative children only)***		
		Late death	Alive at 1yr	P†‡	Late death	Alive at 1yr	P†‡
	(n=543)	(n=48)	(n=139)		(n=14)	(n=315)	
Maternal HIV status							
HIV +	**141/401 (35%)**	19/23 (83%)	88/103 (85%)	0.75	-	29/259 (11%)	-
HIV -	**225/401 (56%)**	1/23 (4%)	4/103 (4%)	1	6/6 (100%)	210/259 (81%)	0.60
Never tested	**35/401 (9%)**	3/23 (13%)	11/103 (11%)	0.72	-	20/259 (8%)	-
If tested, when							
Pre-MOYO	**67/340 (20%)**	2/19 (11%)	24/86 (28%)	0.15	1/6 (17%)	36/220 (16%)	1
At MOYO	**239/340 (70%)**	15/19 (79%)	51/86 (59%)	0.11	4/6 (83%)	164/220 (75%)	0.65
After MOYO	**34/340 (10%)**	2/19 (11%)	11/86 (13%)	1	1/6 (17%)	20/220 (9%)	0.45
If HIV +							
Never had ARVs (incl. on waiting list or not yet eligible)	**76/123 (62%)**	10/17 (59%)	48/76 (63%)	0.74	-	17/27 (63%)	-
Yes, currently on ARVs	**45/123 (37%)**	7/17 (41%)	26/76 (34%)	0.79	-	10/27 (37%)	-
Paternal HIV status							
HIV +	**43/319 (13%)**	6/18 (33%)	24/77 (31%)	0.86	-	13/211 (6%)	-
HIV -	**102/319 (32%)**	2/18 (11%)	5/77 (6%)	0.61	4/5 (80%)	87/211 (41%)	0.16
Never tested	**174/319 (55%)**	10/18 (56%)	48/77 (62%)	0.60	1/5 (20%)	111/211 (53%)	0.20

† Chi2 test. ‡Fisher exact results where expected cell value is less than 5

Table 34 Sibling HIV status & where tested

	HIV serostatus			*Where tested (if tested)*		
	HIV (+)	***HIV (-)***	**Never tested**	**Pre-MOYO**	***On MOYO***	***After MOYO***
Sib 1 (n=289)	2/258 (1%)	55/258 (21%)	201/258 (78%)	13/47 (28%)	14/47 (30%)	20/47 (43%)
Sib 2 (n=242)	4/213 (2%)	43/213 (20%)	166/213 (78%)	13/43 (30%)	8/43 (19%)	22/43 (51%)
Sib 3 (n=161)	1/140 (1%)	29/140 (21%)	110/140 (79%)	10/28 (36%)	5/28 (18%)	13/28 (46%)
Sib 4 (n=94)	2/86 (2%)	16/86 (19%)	68/86 (79%)	5/16 (31%)	2/16 (13%)	9/16 (56%)
Sib 5 (n=45)	2/45 (4%)	6/45 (13%)	37/45 (82%)	1/6 (17%)	2/6 (33%)	3/6 (50%)
Sib 6 (n=17)	0/14 (0%)	5/14 (36%)	9/14 (64%)	1/4 (25%)	1/4 (25%)	2/4 (50%)
Sib 7 (n=8)	0/7	2/7 (29%)	5/7 (71%)	0/2 (0%)	1/2 (50%)	1/2 (50%)
Sib 8 (n=1)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)
ALL (n=857)	**11/764 (1%)**	**157/764 (21%)**	**596/764 (78%)**	**43/147 (29%)**	**33/147 (22%)**	**71/147 (48%)**

5.6.6 TFP-based nutrition education sessions: do they improve knowledge or affect mortality?

Of carers reporting, 230/428 (54%) said they attended nutrition education sessions whilst on MOYO and 198/428 (46%) said they did not. Background maternal education, an important potential confounder, was the same in those who did and those who did not attend the sessions. ***Table 35*** explores whether attendance at the education sessions was associated with differences in knowledge or reported feeding behaviours. It also explores associations between nutrition-related knowledge and long term mortality.

Table 35 Basic nutritional knowledge: is it improved by attending TFP education sessions, and does it affect long term mortality?

	All FUSAM patients	***By attendance of nutrition education sessions on MOYO***			**by long term mortality (as determined at FUSAM visit)**		
		No	Yes	P†	Died	Alive	P†
	(n=543)	(n=198)	(n=230)		(n=64)	(n=462)	
Maternal education							
None	**60/511 (12%)**	23/187 (12%)	23/218 (11%)	0.58	8/62 (13%)	51/433 (12%)	0.80
Primary	**360/511 (70%)**	135/187 (72%)	148/218 (68%)	0.35	45/62 (73%)	303/433 (70%)	0.90
Secondary or more	**91/511 (18%)**	29/187 (16%)	47/218 (22%)	0.12	9/62 (16%)	79/433 (18%)	0.47
Concerning Malawi's "6 food groups"							
Aware that there are 6 groups	**145/388 (37%)**	48/156 (31%)	80/167 (47%)	0.002	17/41 (41%)	126/336 (38%)	0.62
Able to name all 6 food groups	**98/388 (25%)**	35/156 (22%)	53/167 (32%)	0.06	10/41 (24%)	87/336 (26%)	0.84
Unable to name any food group	**156/388 (40%)**	69/156 (44%)	46/167 (28%)	0.002	20/41 (49%)	130/336 (39%)	0.21
Concerning ideal breastfeeding practices							
Correctly states 6 months for starting liquids	**358/482 (74%)**	148/192 (77%)	178/223 (80%)	0.50	27/46 (59%)	328/424 (77%)	0.005
Correctly states 6 months for starting solids	**351/480 (73%)**	143/191 (75%)	175/223 (78%)	0.39	28/46 (61%)	320/422 (76%)	0.03
Correctly states BF should continue until at least 24months	**315/480 (66%)**	118/182 (65%)	160/222 (72%)	0.12	32/47 (68%)	279/421 (66%)	0.80
States that HIV positive mother should stop to BF at 6 months	**290/471 (62%)**	131/187 (70%)	130/219 (60%)	0.03	23/44 (52%)	263/416 (63%)	0.15
Changed feeding practices post-SAM	**152/496 (31%)**	7/196 (4%)	141/224 (63%)	<0.001	14/52 (25%)	138/430 (32%)	0.45

† Chi2 test. ‡Fisher exact results where expected cell value is less than 5

Summarising the table, knowledge of Malawi's "6 food groups" was significantly better among those who attended health education than in those who did not. Carers who were aware of key breastfeeding facts (stated that infants should be breastfed for 6 months before any solids *or* liquids are started – i.e. they correctly described exclusive breastfeeding) were significantly more likely to have children who were alive at long term follow-up. However, this knowledge was not related to attendance at MOYO health education.

Significantly more carers who attended health education reported changing feeding practices since discharge (figure 17 shows details of what changed). This had no obvious effect on long term mortality. Not shown in the table, 21/230 (9%) of those attending education sessions were found to have died at the FUSAM visit and 18/198 (9%) of those not attending also died.

Despite improvements following health education, better knowledge about Malawi's 6 food groups was also not associated with lower long term mortality.

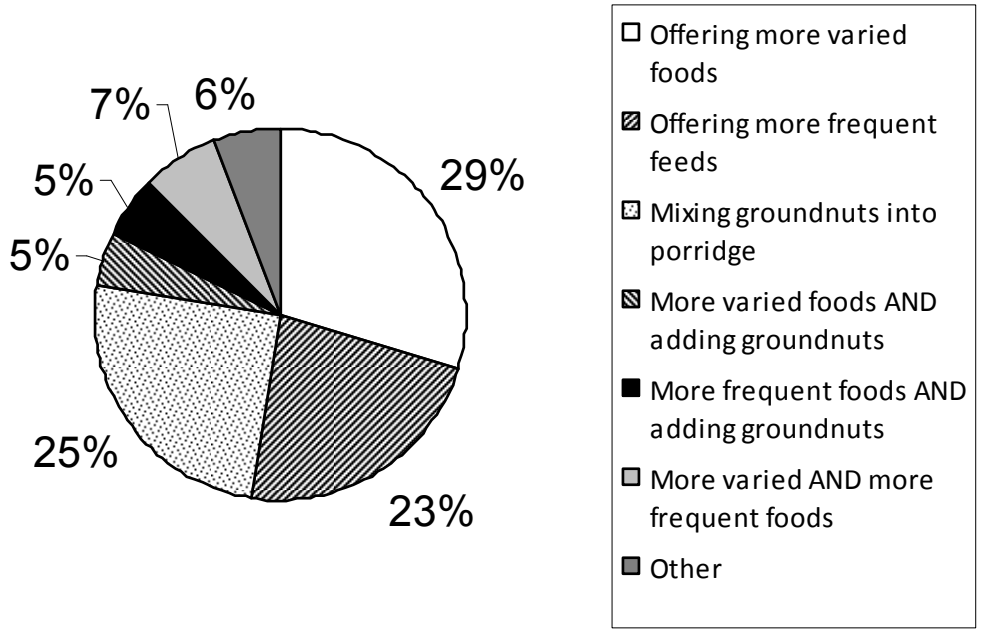


Figure 17 Reported changes in feeding practices (n=152 who reported having changed)

5.7 Results - Growth catch-up in the ex-SAM child

In this section I illustrate anthropometric changes both during and after treatment on MOYO.

5.7.1 Overall z-score changes during treatment

Figure 18 illustrates weight-for-height, weight-for-age and height-for-age z-scores at admission to programme, at OTP discharge (=discharge from programme) and at the long term FUSAM visit. The patterns of change are distinctive:

- ***Weight-for-height*** improves during the programme and continues to improve in children surviving long term. By ≥1 year, average weight-for-height has corrected to the expected population z-score of 0.
- ***Weight-for-age*** also improves during and after treatment. Unlike weight-for-height, there is however a persisting deficit of around -1.8 z-scores at ≥1 year.
- ***Height-for-age*** shows minimal improvement, either during treatment or ≥1 year after treatment.

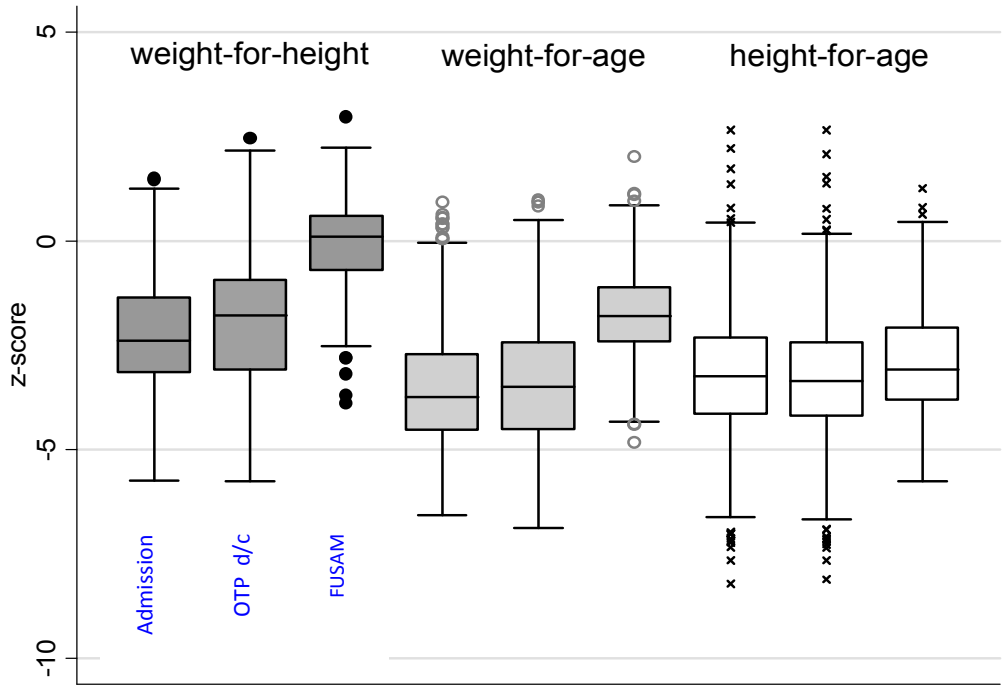


Figure 18 Box plots[‡] showing WHZ, WAZ and HAZ at baseline, OTP discharge and at 1 year follow-up.

WHZ admission (n=976); WHZ OTP discharge (n=966); WHZ 1 year (n=386)
WAZ admission (n=1003); WAZ OTP discharge (n=993); WAZ 1 year (n=386)
HAZ admission (n=992); HAZ OTP discharge (n=982); HAZ 1 year (n=386)
(NB n=386 because not all FUSAM children were available to be measured e.g. if in school)

[‡] In a boxplot: the box shows the upper and lower quartile values; the line in the middle of the box shows the median value; the whiskers show the upper and lower adjacent values (those within a 1.5 inter-quartile range of the nearest quartile); lastly, symbols show any remaining outliers.

The two tables below t-tests comparing Z-score changes from OTP (programme) discharge to final 1 year outcomes.

Unpaired t-tests are presented first to reflect what is shown in the box-plot above. The magnitude of change is greatest for weight-for-height and least for height-for-age. All are statistically significant:

Table 36 Changes in WHZ, WAZ and HAZ from programme discharge to 1 year *(unpaired t-tests)*

	Mean z-score (SD)		**Difference (95% CI)**	**P value**
	At OTP discharge	At 1 year follow-up	*1 year - OTP*	
Weight-for-height (n=966 and 386)	-1.96 (1.5)	-0.04 (1.0)	1.92 (1.76 to 2.08)	<0.0001
Weight-for-age (n=993 and 386)	-3.42 (1.4)	-1.77 (1.1)	1.66 (1.50 to 1.82)	<0.0001
Height-for-age (n=983 and 386)	-3.34 (1.4)	-2.97 (1.4)	0.37 (0.21 to 0.53)	<0.0001

Paired t-tests better reflect individual level changes and are shown in ***table 37***. Magnitude of these individual-level changes are less than for the groups as a whole. Increases in WHZ and WAZ from OTP discharge to 1 year follow-up are still statistically significant. HAZ changes are not:

Table 37 Changes in WHZ, WAZ and HAZ from programme discharge to 1 year ***(paired t-tests)***

	Mean z-score (SD)		**Difference (95% CI)**	**P value**
	At OTP discharge	At 1 year follow-up	*1 year - OTP*	
Weight-for-height (n=386)	-1.16 (1.1)	-0.04 (1.0)	1.11 (0.99 to 1.23)	<0.0001
Weight-for-age (n=386)	-2.64 (1.2)	-1.77 (1.1)	0.87 (0.77 to 0.98)	<0.0001
Height-for-age (n=386)	-3.03 (1.3)	-2.97 (1.3)	0.05 (0.04 to 0.15)	0.27

5.7.2 Z-score changes during treatment, by HIV status and admission diagnosis

Boxplot 19 follows the same format as ***figure 18***: WHZ, WAZ and HAZ at admission, at OTP (programme) discharge and at long term FUSAM follow-up. Differences in z-score changes by HIV status are illustrated first.

a) Changes by HIV status

Patterns of change by HIV are similar to overall patterns of change. WHZ, WAZ and HAZ at admission and OTP discharge are all higher in HIV negative patients than in HIV positives. By ≥1 year (see also ***table 38***):

- WHZ has recovered to the reference population mean of 0 in both HIV negative and positive groups.
- WAZ has significantly improved ($p<0.01$) in both HIV negative and positive patients but both groups remain below the reference population mean, WAZ zero.
- HAZ is the most depressed anthropometric index in both HIV positive and negative patients. There is no improvement following OTP discharge among HIV negative patients. There is small but statistically significant improvement among HIV positive patients (a HAZ improvement of 0.37 z-scores, $p<0.01$)

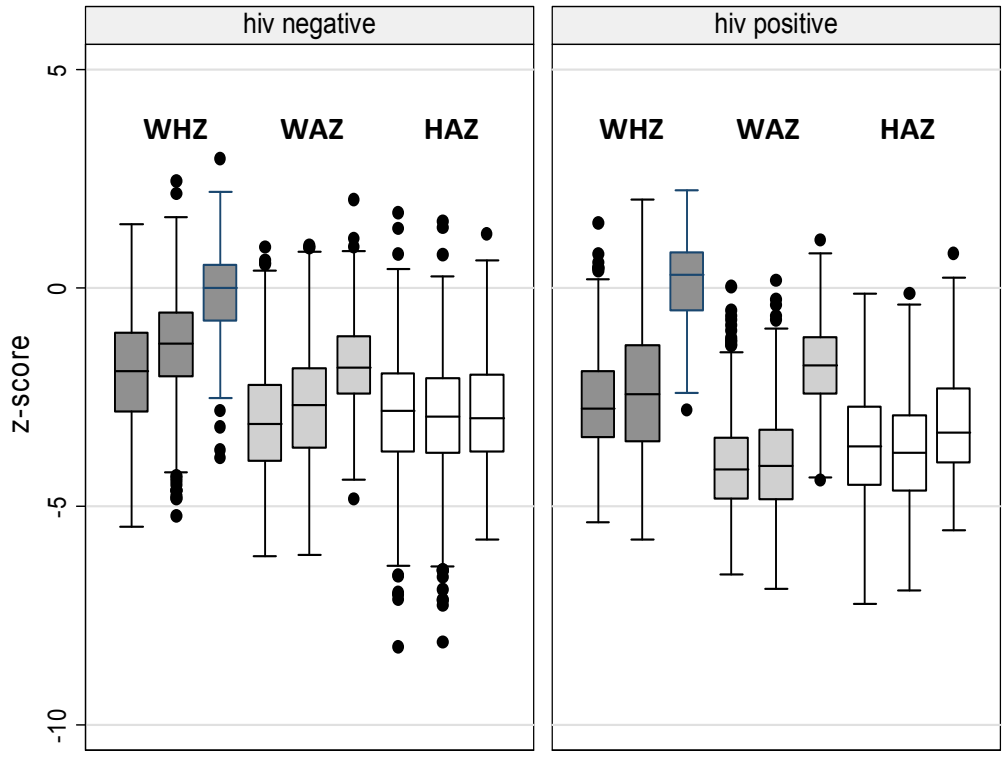


Figure 19 Box plots showing baseline, OTP and 1 year WHZ, WAZ and HAZ, *by HIV status*

Table 38 presents formal statistical testing of the changes that can be observed in the box-plot on the previous page.

Table 38 WHZ, WAZ and HAZ changes from OTP discharge to 1 year follow-up, by HIV *(paired t-test)*

	Mean z-score (SD)		Difference (95% CI)	P value
	At OTP discharge	At 1 year follow-up	*1 year - OTP*	
Weight-for-height				
in HIV ⊖ (n=268)	-1.07 (1.1)	-0.12 (1.0)	0.95 (0.82 to 1.08)	<0.0001
in HIV ⊕ (n=112)	-1.32 (1.2)	0.14 (1.0)	1.46 (1.21 to 1.72)	<0.0001
Weight-for-age				
in HIV ⊖ (n=269)	-2.45 (1.1)	-1.77 (1.1)	0.68 (0.57 to 0.78)	<0.0001
in HIV ⊕ (n=112)	-3.06 (1.1)	-1.74 (1.0)	1.31 (1.08 to 1.55)	<0.0001
Height-for-age				
in HIV ⊖ (n=268)	-2.83 (1.3)	-2.90 (1.3)	-0.08 (-1.19 to 0.03)	0.15
in HIV ⊕ (n=112)	-3.51 (1.2)	-3.13 (1.3)	0.37 (0.18 to 0.57)	0.0002

b) Changes by admission problem (oedematous or non-oedematous malnutrition)

Oedematous and non-oedematous malnutrition reflect different underlying patho-physiology. Oedema also affects admission weight and thus admission weight-for-height and weight-for-age. In this section therefore I examine whether initial oedema has any longer term impact on z-score changes. Results in **figures 20 and 21** are presented stratified by underlying HIV serostatus.

Patterns and magnitudes of z-score changes split by oedematous or non-oedematous malnutrition are similar to overall patterns of change.

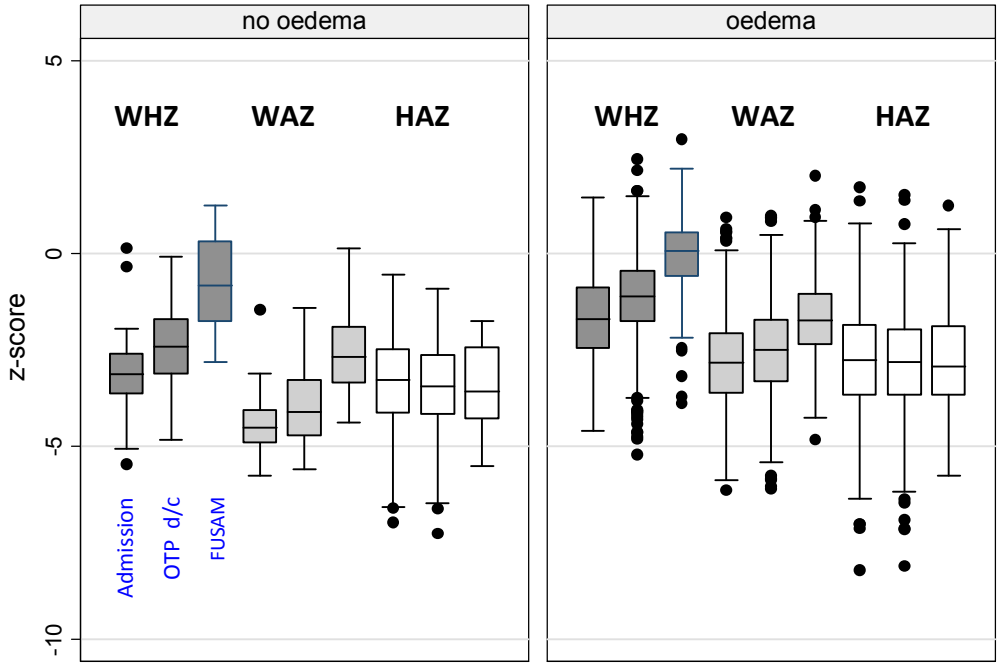


Figure 20 Box plots showing baseline, OTP and 1 year WHZ, WAZ and HAZ, *by admission oedema, in HIV seronegative patients*

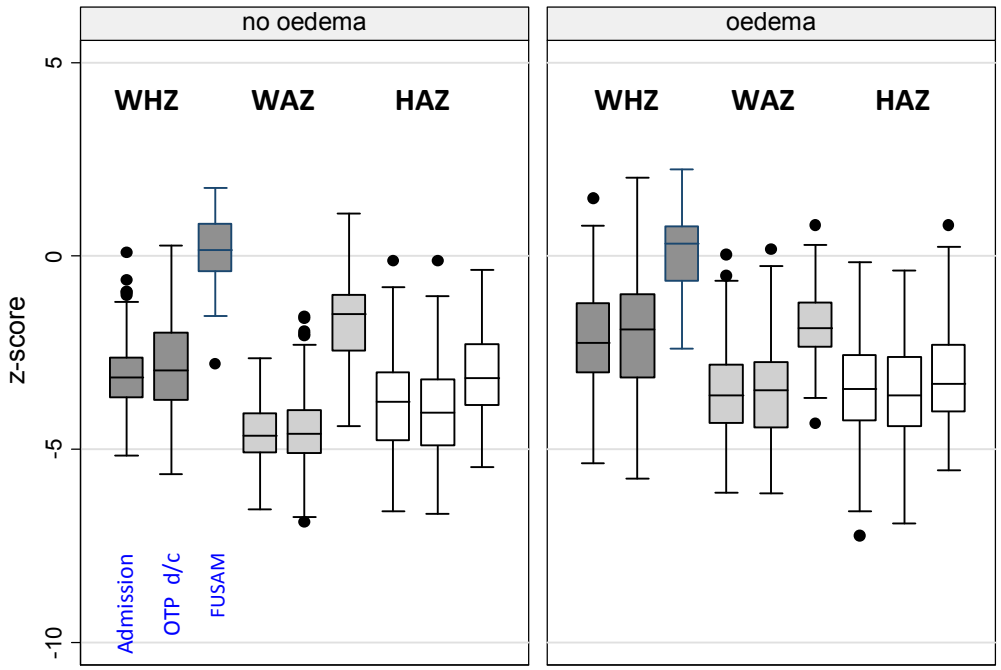


Figure 21 Box plots showing baseline, OTP and 1 year WHZ, WAZ and HAZ, *by admission oedema, in HIV seropositive patients*

5.7.3 Weight-for-height changes during treatment

The line graphs below show how weight-for-height of individual children changes over during and in the year following treatment. In both HIV seropositive and negative patients there is an initial dip in WHZ (corresponding mainly to loss of oedema) followed by steady rise thereafter. The importance of pair-wise tests of change is clear: whilst overall WHZ is greater at 1 year than at OTP, but this is not true for all children. Greater magnitude of catch-up is also evident for HIV positive survivors to 1 year.

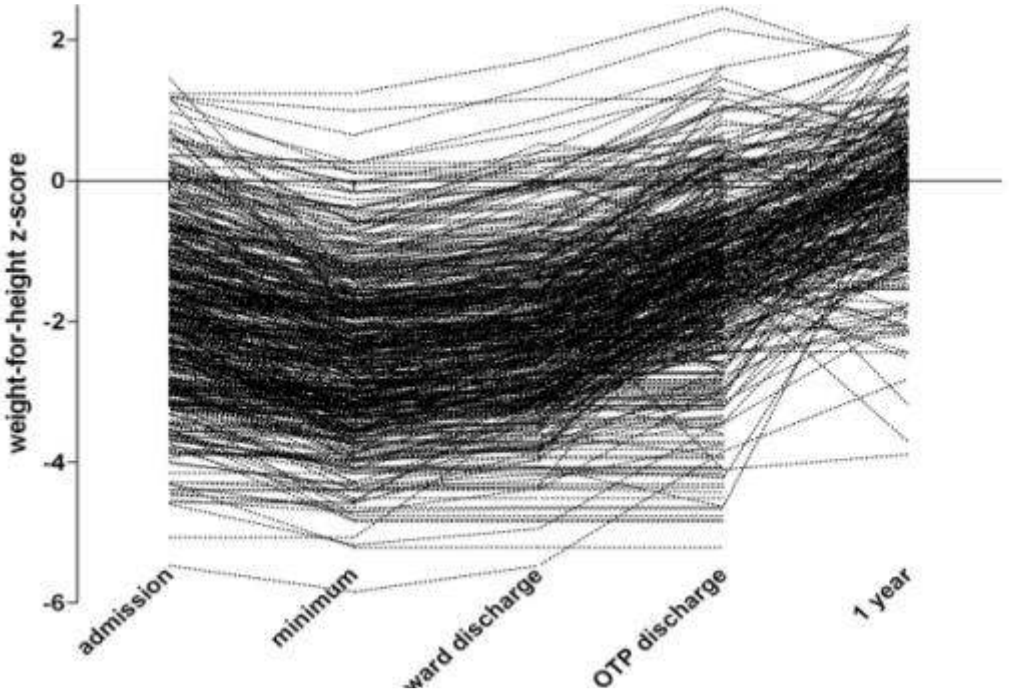


Figure 22 Weight-for-height z-scores in HIV seronegative children

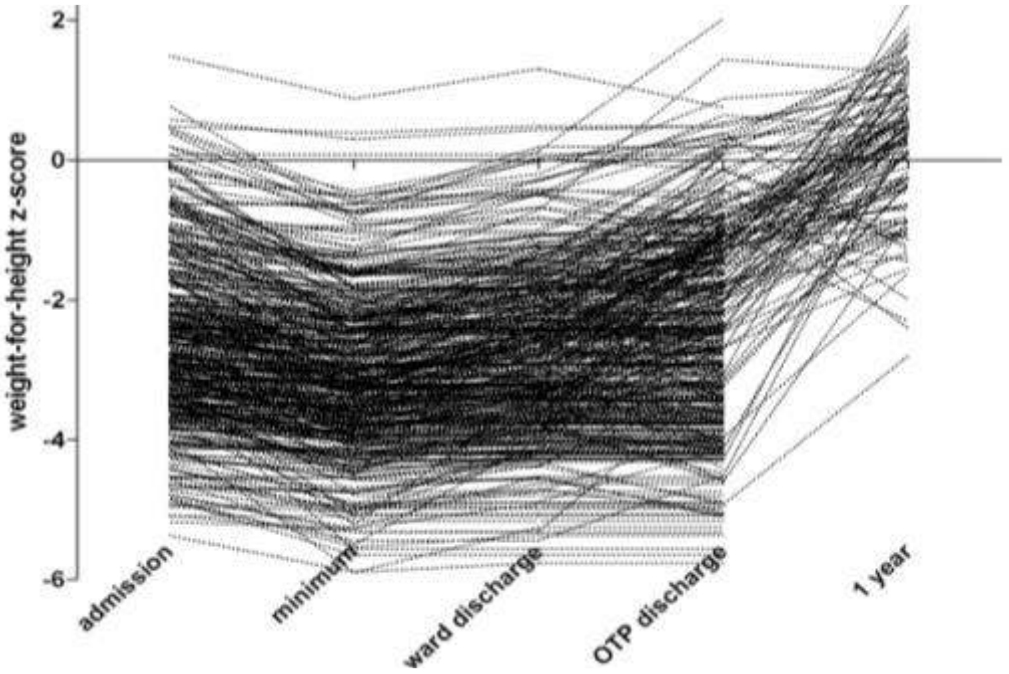


Figure 23 Weight-for-height z-score changes in HIV seropositive children

N.B. The x-axis in these graphs is not directly proportional to time. In particular, the 'gap' from 'OTP discharge' to '1 year' should ideally be larger than the other periods to reflect the greater duration. This has not been possible to represent visually so I ask the reader to kindly be aware of the scaling constraint.

5.7.4 Weight-for-age changes during treatment

As with weight-for-height, the two line graphs below show an initial decrease in weight-for-age followed by a steady rise thereafter. Again the magnitude of 1 year catch-up is greater in HIV seropositive than in seronegative patients. Numbers surviving to 1 year are however less in HIV seropostive patients. The persisting weight-for-age is also evident in both groups.

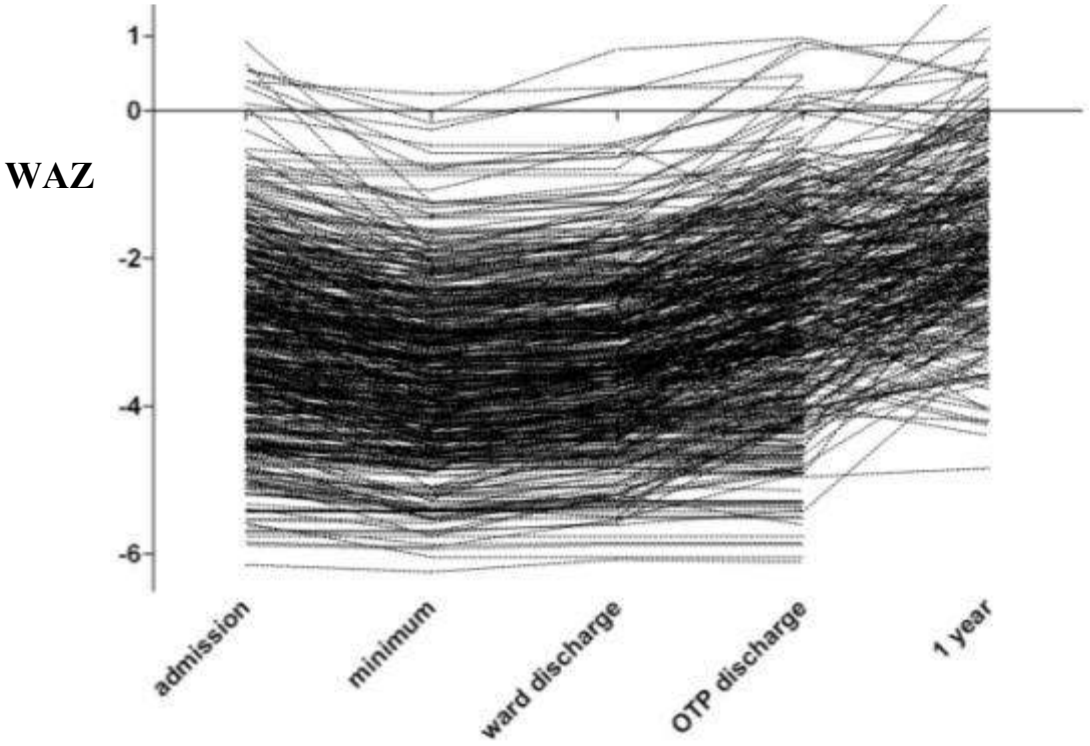


Figure 24 Weight-for-age z-score changes in HIV seronegative children

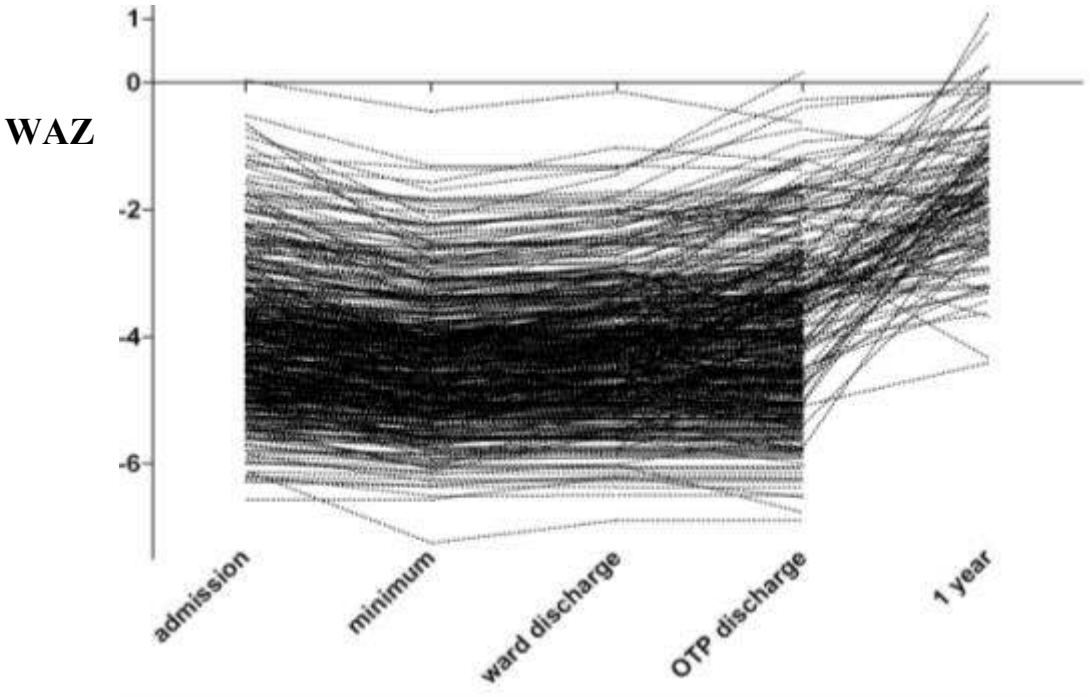


Figure 25 Weight-for-age z-score changes in HIV seropostive children

5.7.5 Height-for-age changes during treatment

To complete the nutritional profile from sections 5.7.3 and 5.7.4, height-for-age changes are shown in ***figures 26*** and ***27***. HAZ remains relatively static during initial phases of treatment. By OTP discharge and at 1 year a large range very mixed changes are observed: some children's height-for-age z-score increasing and other's decreasing. There is no consistent pattern. Among those whose height-for-age increases, very few recover to 0, the expected population height-for-age z-score.

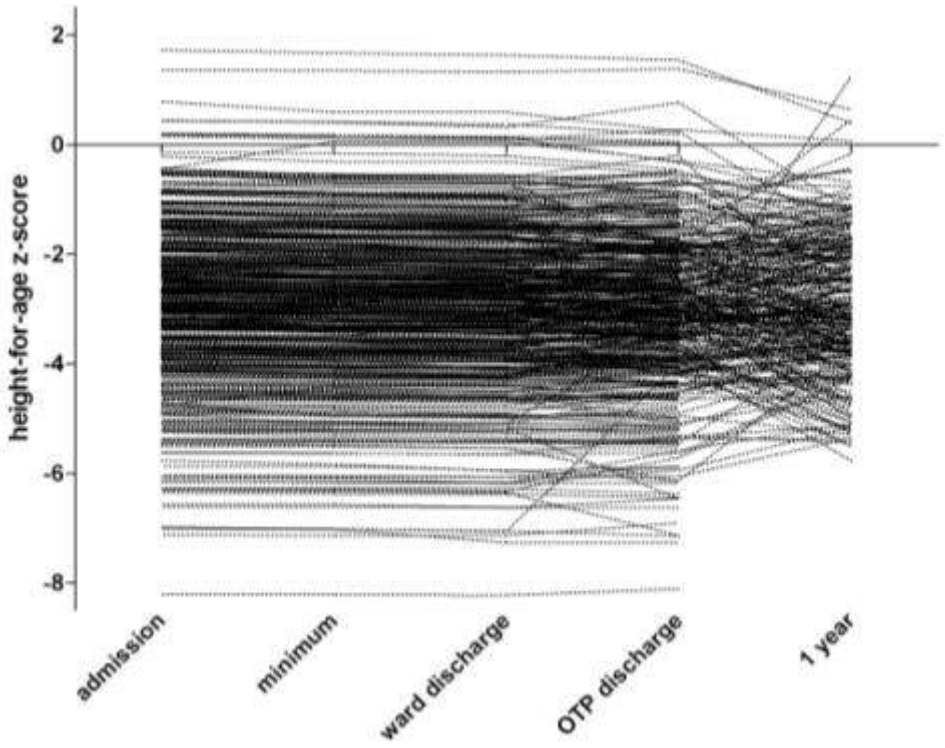


Figure 26 Height-for-age z-score changes in HIV seronegative children

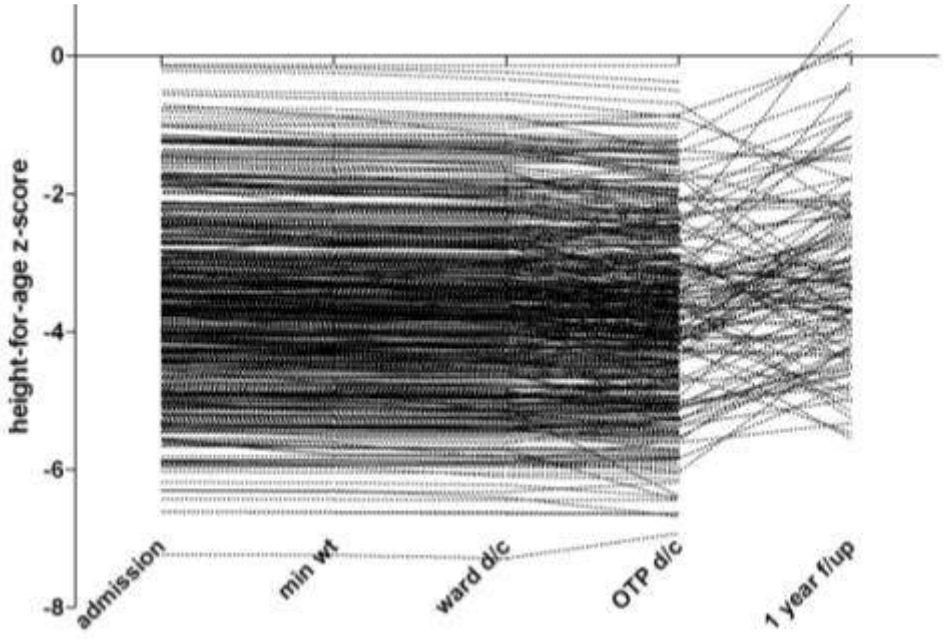


Figure 27 Height-for-age z-score changes in HIV seropostive children

5.8 Results - Growth catch-up compared to sibling controls

5.8.1 Weight-for-height, weight-for-age and height-for-age compared to sib controls

Figure 28 and ***table 39*** show weight-for-height, weight-for-age and height-for-age of the ex-MOYO child and sibling controls, both measured at FUSAM visit. Over 90% of siblings were reported never having SAM. There are notable differences according to anthropometric index:

- Weight-for-height is similar in the ex-MOYO child and sibling controls. Both are close to the population reference z-score of 0.
- Weight-for-age low in both groups, over one standard deviation below the reference population mean. It is lowest in ex-MOYO children. As a group, these are 0.5 z-scores, significantly below, sibling controls.
- Height-for-age is also low in both groups. It is lowest in ex-MOYO children, who are almost 3z scores below reference median and over 1z score, significantly below, sibling controls.

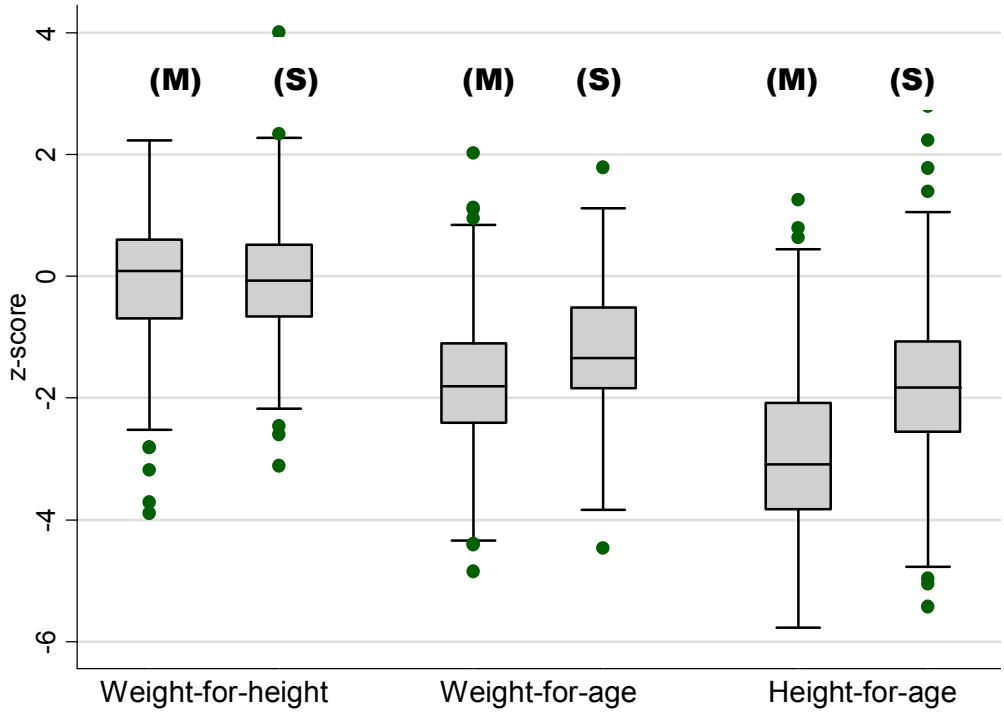


Figure 28 Boxplot showing weight-for-height, weight-for-age and height-for-age of the ex-MOYO child (M) compared to sibling controls (S). n(MOYO)=386. n(sibling controls)=277

Table 39 Weight-for-height of the ex-MOYO child compared to sibling controls (unpaired t-test)

	Mean weight-for-height z-score (SD)		Difference (95% CI)	*P value*
	MOYO child (M) N=386	***Sibling (S) N=277***	**M – S**	
Weight-for-height	-0.04 (1.0)	-0.07 (0.9)	0.03 (-0.12 to 0.19)	0.69
Weight-for-age	-1.77 (1.1)	-1.22 (1.1)	-0.55 (-0.71 to -0.38)	<0.0001
Height-for-age	-2.97 (1.3)	-1.83 (1.4)	-1.13 (-1.34 to -0.93)	<0.0001

5.8.2 Weight-for-height compared to sib controls, by birth order

The boxplot and table below explore the hypothesis that size may depend upon birth order. The MOYO child is presented first for simplicity: 257/925(28%) were actually firstborns. Of the others, 242/925(26%) were second-born, 188(20%) third-born and 238(26%) fourth-born or later.

It can be seen that weight-for-height of ex-MOYO child is similar to that of all siblings, no matter what their birth order. Paired t-tests in table 40 confirm no significant differences between the MOYO child and individual siblings in the same family. An ANOVA test of multiple means, together with Scheffe's multiple comparison test gives similar results. All groups have a z-score close to the reference population mean of zero.

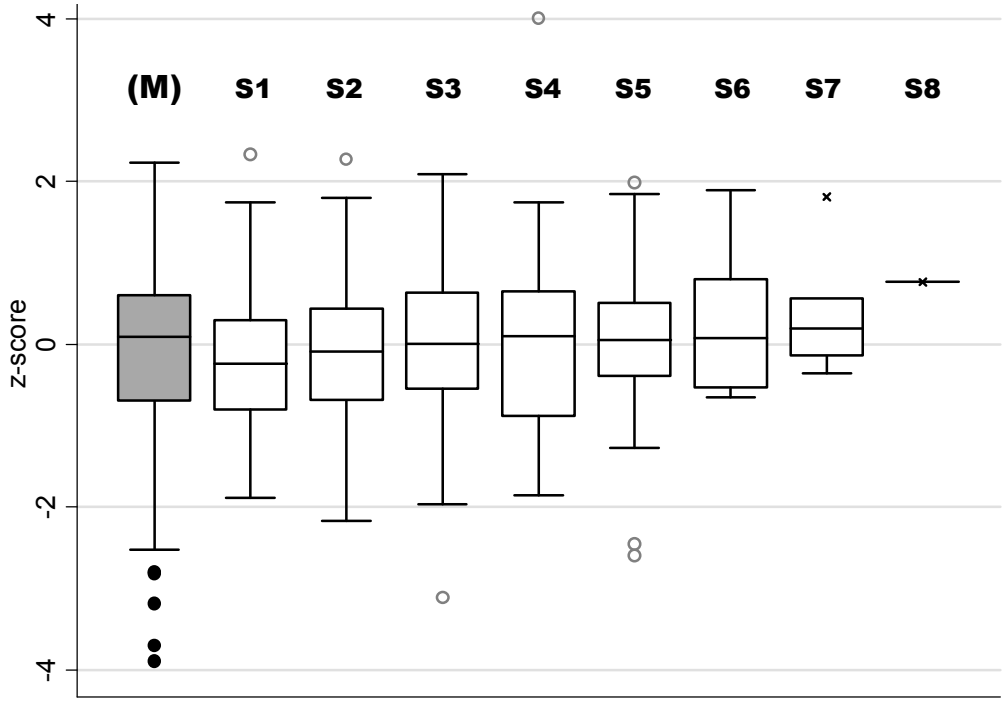


Figure 29 Boxplot showing weight-for-height of the MOYO child at 1 year compared to sibling controls. **(M)** = ex MOYO child; **S1** = firstborn child in the family; **S2** = second-born child etc.

Table 40 Weight-for-height of the ex-MOYO child compared to sibling controls (paired t-tests)

	Mean weight-for-height z-score (SD)		Difference (95% CI)	*P value*
	MOYO child (M)	*Sibling (S)*	M – S	
Sib 1 (n=53)	-0.068 (1.1)	-0.24 (0.8)	0.17 (-0.15 to 0.50)	0.28
Sib 2 (n=68)	0.04 (1.0)	-0.08 (0.9)	0.12 (-0.16 to 0.40)	0.38
Sib 3 (n=54)	-0.00 (0.8)	-0.09 (0.9)	0.08 (-0.22 to 0.39)	0.57
Sib 4 (n=25)	-0.43 (1.0)	0.12 (1.3)	-0.55 (-1.20 to 0.10)	0.09
Sib 5 (n=22)	0.04 (1.2)	0.10 (1.0)	-0.05 (-0.64 to 0.53)	0.85
Sib 6 (n=8)	-0.17 (1.2)	0.24 (0.9)	-0.41 (-1.43 to 0.60)	0.36
Sib 7 (n=6)	-0.32 (1.7)	0.35 (0.8)	-0.67 (-2.95 to 1.60)	0.48
Sib 8 (n=1)	0.78	0.77	0.01	-

5.8.3 Weight-for-age compared to sib controls, by birth order

Following the same format, weight-for-age z-scores are shown below. Two points are important:

a) Median weight-for-age of all children in the family is low.

b) Weight-for-age z-score of ex-MOYO children is lower than that of sibling controls, irrespective of their birth order. Paired t-tests in table 41 show statistically significant differences. Similar results are obtained using ANOVA multiple mean comparisons or non-parametric Wilcoxon signed-rank tests.

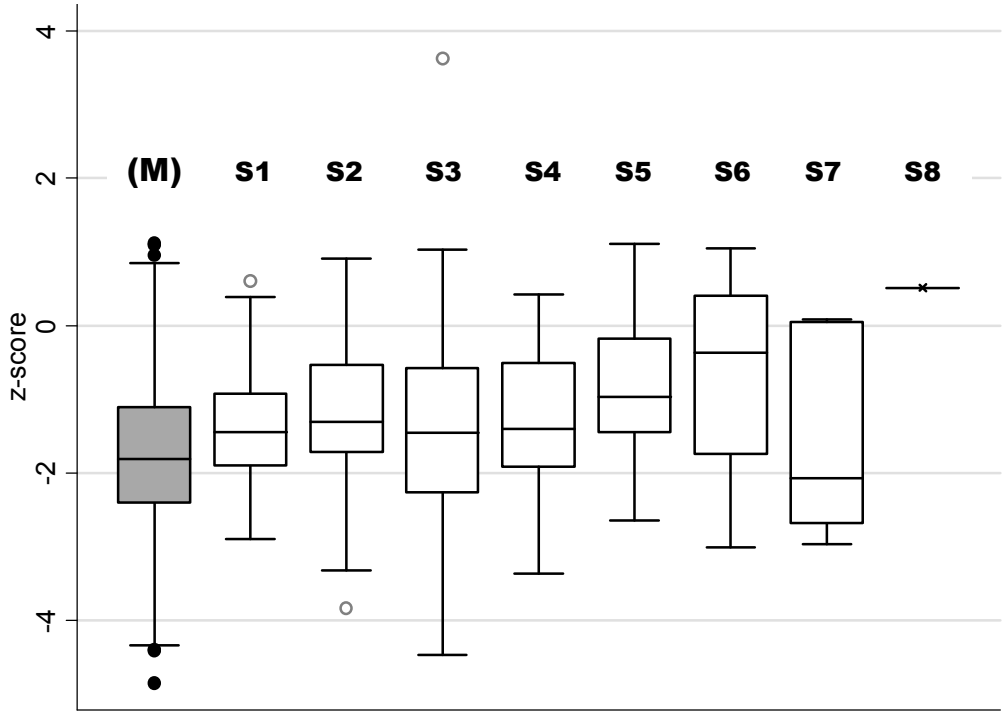


Figure 30 Boxplot showing weight-for-age of the MOYO child at 1 year compared to sibling controls. **(M)** = ex MOYO child; **S1** = firstborn child in the family; **S2** = second-born child etc.

Table 41 Weight-for-age of the ex-MOYO child compared to sibling controls *(paired t-tests)*

	Mean weight-for-age z-score (SD)		Difference (95% CI)	*P value*
	MOYO child (M)	*Sibling (S)*	M – S	
Sib 1 (n=53)	-1.82 (1.3)	-1.35 (0.9)	-0.47 (-0.78 to -0.16)	0.003
Sib 2 (n=68)	-1.76 (1.1)	-1.11 (1.0)	-0.64 (-0.91 to -0.38)	<0.0001
Sib 3 (n=54)	-1.82 (0.9)	-1.41 (1.3)	-0.41 (-0.76 to -0.62)	0.02
Sib 4 (n=25)	-2.33 (1.1)	-1.27 (0.9)	-1.07 (-1.66 to -0.48)	0.001
Sib 5 (n=22)	-1.71 (1.2)	-1.00 (1.0)	-0.71 (-1.30 to -0.12)	0.02
Sib 6 (n=8)	-2.05 (1.3)	-0.67 (1.6)	-1.38 (-2.74 to -0.02)	0.05
Sib 7 (n=6)	-1.96 (1.5)	-1.2 (1.3)	-0.76 (-2.85 to 1.33)	0.39
Sib 8 (n=1)	-0.11	0.51	-0.63	-

5.8.4 Height-for-age compared to sib controls, by birth order

Again following the same format, height-for-age z-scores of ex-MOYO children compared to sibling controls are shown. Two points are notable:

a) Height-for-age of all children is low. It is approximately 2 z-scores below normal for firstborn though to fifth-born sibs. Group sizes of sibs 6, 7 and 8 are too small to comment.

b) Height-for-age of ex-MOYO children is lower than that of sibling controls, Paired t-tests in ***table 31*** show statistically significant differences. Similar results are obtained using either ANOVA with Scheffe's multiple comparison test or non-parametric Wilcoxon signed-rank tests. Height-for-age deficit in the ex-MOYO child is more marked than the weight-for-age deficit and ranges from 0.8 to over 1.6 z-scores.

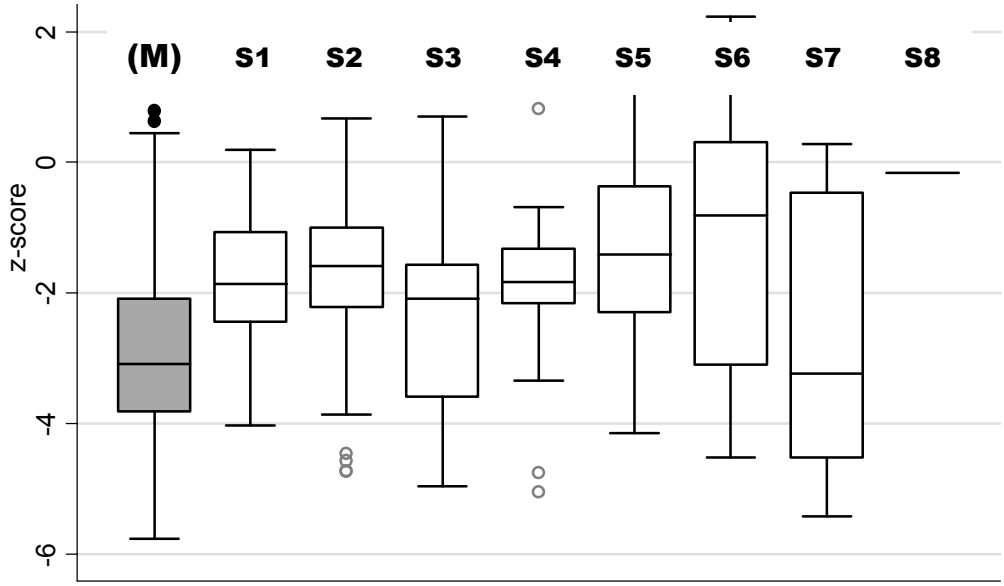


Figure 31 Boxplot showing height-for-age of the MOYO child at 1 year compared to sibling controls. **(M)** = ex MOYO child; **S1** = firstborn child in the family; **S2** = second-born child etc.

Table 42 Height-for-age of the ex-MOYO child compared to sibling controls *(paired t-tests)*

	Mean height-for-age z-score (SD)		Difference (95% CI)	*P value*
	MOYO child (M)	*Sibling (S)*	M – S	
Sib 1 (n=53)	-3.09 (1.2)	-1.78 (1.1)	-1.31 (-1.68 to -0.95)	<0.0001
Sib 2 (n=68)	-3.08 (1.2)	-1.66 (1.2)	-1.43 (-1.77 to -1.09)	<0.0001
Sib 3 (n=54)	-3.06 (1.0)	-2.24 (1.6)	-0.83 (-1.24 to -0.41)	0.0002
Sib 4 (n=25)	-3.54 (1.3)	-1.95 (1.2)	-1.59 (-2.26 to -0.93)	<0.0001
Sib 5 (n=22)	-3.03 (1.0)	-1.64 (1.2)	-1.39 (-2.00 to -0.77)	0.0001
Sib 6 (n=8)	-3.35 (1.3)	-1.19 (2.2)	-2.16 (-4.13 to 0.18)	0.04
Sib 7 (n=6)	-3.30 (0.9)	-2.50 (2.0)	-0.80 (-2.76 to 1.16)	0.34
Sib 8 (n=1)	-1.21	-0.16	-1.04	

Chapter 6

DISCUSSION

Since they address two distinct factors underlying SAM outcomes, PRONUT and FUSAM will first be discussed in separate sections. A final conclusion will draw together final implications of both studies.

6.1 PRONUT

6.1.1 Key findings

In the MOYO setting, Synbiotic2000 Forte™, prescribed in RUTF at an average daily dose of $>10^{10}$ organisms per day, had no significant effect improving pre-specified nutritional or clinical outcomes from SAM. Even though negative, this is an important finding. PRONUT is, to my knowledge, one of the largest probiotic/prebiotic RCTs to date. It is also one of very few based in a low-income, high mortality, developing country. Putting the 795 patients in context, a 2004 Cochrane review of probiotics in the treatment of diarrhoea included 1917 patients from 23 studies, only 2 of which were set in "high child and adult mortality" countries[59]; a 2006 Lancet meta-analysis of probiotics in diarrhoea prevention had 4844 patients from 34 trials, only 1 of which was developing country and community based[60].

A post-hoc observation of reduced outpatient mortality amongst children receiving Synbiotic is interesting. If true, it is also important clinically. I emphasise that this observation should not be over-interpreted, but do believe that it justifies further research.

6.1.2 Strengths and weaknesses

Study strengths

Biological plausibility of observed results

A lack of Synbiotic efficacy for SAM inpatients might be because these children are the most vulnerable, with greatest impairment of all physiological systems[72]. Some causes of early death are unlikely to be affected by known Synbiotic actions e.g. re-feeding syndrome and electrolyte imbalance[100],[101].

Possible benefits for children surviving inpatient care is consistent with known Synbiotic effects like immune stimulation and improved gut environment and integrity. These take time and cannot occur until organ, cellular and immune functions have begun to recover. Such recovery would be greatest in outpatients after initial discharge – as was observed. Repeat admissions, which imply repeat episodes of severe illness would dilute any inter-group differences - also consistent with observed results, where outpatient differences are most pronounced during 1st episode of outpatient care but attenuated when all subsequent admission episodes are taken into account.

Antibiotics may also plausibly modulate the observed inpatient/outpatient differences. In-vitro testing showed cotrimoxazole sensitivity in 2 of 4 Synbiotic organisms. Following standard protocols, all inpatients received cotrimoxazole. Half also had parenteral antibiotics. Children who were HIV seropositive continued on long term cotrimoxazole prophylaxis after ward discharge during and after outpatient treatment. Antibiotics may have reduced gut colonization by and hence efficacy of Synbiotic. In contrast, HIV negative outpatients, in whom the possible outpatient Synbiotic effect was strongest, received no antibiotics.

Use of definitive outcomes for maximal relevance and applicability to developing country SAM settings

Hard outcomes like nutritional cure and death are rare in functional food studies[60],[102]. Examining them, PRONUT stands out as directly relevant to nutrition policy makers; to programme managers[88]; and, most importantly, to families and communities whose children die as a result of SAM[103].

Generalizability

For maximal generalizability to 'real world' nutrition programmes, PRONUT was set in a government hospital providing routine service work. A key decision was to enrolled a typical rather than selected patient caseload[104]. Included were children with disabilities and other conditions whose growth patterns are commonly abnormal[105]. PRONUT was powered to explore both whole-group and sub-group effects.

Minimal losses to follow-up

Another strength of the study was that we found final outcome for all but 26/795 (3.2%) of randomised patients. This was made possible because of the efforts of a dedicated community team and minimises the follow-up bias which is a common problem for field based studies in developing countries.

Safety

In MOYO's high-risk patients, no excess sepsis, particularly no Synbiotic-associated sepsis, is important. No excess mortality was observed, as was discussed in one recent study on

probiotics/prebiotics in severe pancreatitis[106]. Increased inpatient vomiting, severe diarrhoea and cough, and a non-significant increase in inpatient mortality were noted. One explanation for these observations is chance. Known probiotic effects do not offer a clear explanatory mechanism for these findings. Increased severe diarrhoea may be due to osmotic effect of prebiotics. It would be interesting therefore for future studies to distinguish prebiotic and probiotic effects. With continued careful monitoring of risks as well as benefits, we believe that further work using these functional foods in HIV and SAM is justified.

Study weaknesses

Several limitations could also explain the predominantly negative results:

Synbiotic sharing and cross contamination

Though inter-group RUTF sharing was discouraged, it cannot be excluded. Faeco-oral probiotic cross-contamination was also possible[107]. Dilution of true group differences would result. Such sharing and contamination would be maximal whilst patients were living closely together during inpatient care. It would be minimal during home-based treatment as close neighbours on different groups are unlikely. This would also plausibly explain our observed trends towards group differences during outpatient treatment alone.

Synbiotic specificity

Probiotics and prebiotics are large and diverse groups, each with specific effects in specific patients. This heterogeneity, combined with a paucity of other data on their use in the treatment of SAM, makes comments on the consistency of PRONUT findings with other studies difficult. Relevant to this current study, previous work (using *Bifidobacterium bifidum* with *Streptococcus thermophilus* probiotics) found an effect on CD4 and diarrhoea in HIV positive patients[108]; whilst another study (using *Lactobacillus GG*) have found no effect in healthy Malawian children[109]. Hoping to demonstrate proof of principle in SAM, PRONUT used a probiotic/prebiotic with a proven track record in other patient groups[91],,[110],[92]. Another formulation might have shown different results.

Possible suboptimal Synbiotic dose

Probiotics have approximately linear dose-response effects, at least on diarrhoea outcomes. The commonly accepted efficacy 'threshold' is $>10^8$ organisms per day [102]. Regular quality control checks showed that *prescribed* doses were $>10^{10}$ CFU per day, comfortably above this lower limit. Higher doses are possible in principle, but might not be possible in practice given the cost of a log unit dose increase. Also perhaps responsible for negative results is a suboptimal *consumed* dose of RUTF (and thus of Synbiotic mixed into the RUTF). This might have happened at home if carers

shared the RUTF with other children. PRONUT had only carer reports rather than direct observation to confirm non-sharing and compliance. Adequate weight gain was however also consistent with the RUTF being eaten rather than shared to any important extent.

Synbiotic dose regime & gut colonization

Probiotics are often ingested as a single large bolus dose. PRONUT patients consumed RUTF (and thus Synbiotic) in divided amounts spread throughout the day. Probiotic effects depend on successful transit through the upper gastrointestinal (GI) tract to sites of action in the small and large intestines. Some probiotic organisms always die during transit. Larger single doses (perhaps timed away from antibiotic administration – there was occasionally overlap with our regime) might have colonized the gut better and had more effect. Resources were unavailable to directly confirm the success of the PRONUT regime and adequate colonization had to be assumed based on other research[107]. It is plausible in SAM given the fact that gastric acidity, normally a barrier to live probiotic transit, is reduced.

Prebiotic effects

The four prebiotics in Synbiotic may have caused non-specific overgrowth of enteric flora which mitigated against the probiotic component. Unfortunately stool cultures were not done to test this possibility. This is another issue for future research: probiotics alone or pro/prebiotic combinations for malnutrition?

Lack of clinical effects

Clinical effects like reduced diarrhoeal or respiratory symptoms would have been consistent with known probiotic effects. Clinical effects might also have suggested mechanisms for the possible reduction in outpatient mortality. One isolated outpatient finding was reduced severe diarrhoea – though again patient numbers were small. Beneficial clinical manifestations make a true outpatient mortality effect more likely - but equally their absence does not exclude a true effect. Benefits can be subtle, at immune system level for example. Another possibility is that true symptom differences were missed, obscured by the noise inherent to any self-reported variable. Group imbalances in days of outpatient observation might also have played a role. To address such limitations, future work might add laboratory-measured clinical response indicators[108].

Unbalanced groups at entry to outpatient care

At randomization, groups appeared well balanced. Minor differences at point of entry to outpatient care (lower % HIV; less malnourished according to WHZ in the Synbiotic group) raise the possibility of confounding or bias at this point

6.1.3 Meaning of the study and implications for future policy and research

Overall outcomes observed in PRONUT study highlight the need for effective, evidence-based SAM interventions. Control group cures were low, 51.3%(203/396) and deaths high, 30.0%(119/396). Such statistics are unfortunately not unusual[46],[4],[53]. HIV and late presentation to care, with complications of SAM already present are major factors underlying these poor outcomes. In this setting, Synbiotic2000 Forte™, prescribed in RUTF at an average daily dose of $>10^{10}$ organisms per day did not improve outcomes from current therapies. There is therefore no evidence at present, either from PRONUT or from other studies, to recommend routine use of functional additives to standard RUTF.

An observation of reduced mortality in Synbiotic outpatients is important to explore in future studies. Since PRONUT was not designed to look at outpatients alone, bias, confounding or chance cannot be excluded as an explanation for this finding. An effect is however biologically plausible. SAM associated enteropathy is a particularly important problem which probiotics may address. Since PRONUT was published, a 'viewpoint' article in the Lancet argued that enteropathy may account for a far greater proportion of malnutrition than currently recognised[111]. If true, this would make future exploration of other functional additives even more important: not just for children with SAM but for those with other less acute but more prevalent forms of malnutrition[112]. Future studies using probiotics in malnutrition should focus on randomising SAM outpatients and possibly even children with moderate malnutrition, whose treatment is receiving increasing international interest. Such research would nest well in CMAM (Community Management of Acute Malnutrition) programmes, which focus on early identification and outpatient treatment of children with malnutrition. In discussing current results, this is exactly the patient group who might benefit most from any true probiotic/prebiotic effects.

6.2 FUSAM

6.2.1 Key findings

In the HIV prevalent MOYO setting, overall SAM mortality is markedly above SPHERE targets of <10%[88]. In total, 427/1024 (41%) of children admitted for treatment are known to have died. Mortality was highest during initial inpatient treatment: 23%(238/1024). In **FUSAM,** 8%(84/1024) more died within 90 days of admission and 10%(105/1024) during long term follow-up. These FUSAM deaths may not have been noted by many nutrition programmes which only monitor patients in the short and medium term.

To properly interpret these results, it is important to note key subgroups. Though still short of SPHERE standards, these give a much more optimistic perspective of TFP performance:

- Mortality probability among HIV negative patients is 19% (95% CI 15 to 23%) overall. This compares to overall 69% (63 to 74%) 2 years mortality for HIV positive patients.
- Late mortality is less among HIV negative patients than among HIV positive. 90 day HIV negative mortality is 13%(11 to 17%) and rises by 6%. This contrasts a 23% rise in HIV positive mortality, from the 90 day 'baseline' of 46% (42 to 51%).
- If a child achieves initial programme cure, the chances of long term survival are good: 365/471 (77%) of cures were still alive at a year or more after their first admission.

HIV was the biggest single risk factor for both short and long term mortality, associated with over 4 times the hazard of death. Increased severity of wasting and underweight at original admission were also significantly associated with increased total mortality as well as increased 90 day mortality. Oedematous patients were less likely to die both short and long term. This contrasts some historical studies where kwashiorkor was associated with excess mortality[26]. It may reflect differences in the local pathophysiology of kwashiorkor, but equally may just be due to greater awareness and hence earlier presentation of oedematous malnutrition in Malawi. Age was a risk factor only in <12 month age group, whose hazards were 2.3 times above the reference 48-60 month age group (adjusting for oedema, HIV and admission anthropometry)

Mortality hazards for other potential risk factors varied by HIV status and timing of death. Due to the large number of risk factors explored results should be interpreted with care: by chance alone 1 in 20 will be statistically significant. Underlying disability was the most striking, biologically plausible risk factor for both short and long term mortality in both HIV positive and negative children. Others, including HIV staging and severity of symptoms prior to admission were not clearly and consistently associated with death. Parental education, occupation and family socioeconomic status also did not independently affect mortality.

The long term anthropometric profile of survivors was mixed. Mean weight-for-height z-score of children still alive had recovered almost to NCHS reference mean: -0.04(SD1.0, n=386). This compares to baseline of -1.16(SD1.0). Height-for-age z-score remained low and unchanged: -2.97(SD 1.3) compared to -3.03(SD 1.4) at baseline. Putting these in context, mean sibling weight-for-height was -0.07(SD 0.9, n=277) and height-for-age -1.83(SD 1.4, n=277). A fertile area for future work is to explore these differences: could different interventions have led to better catch-up growth (especially focusing on HAZ catch-up? Why does one child in a family but not another develop overt malnutrition? Which packages of care could be developed to better benefit the whole family? (noting for example the low uptake of HIV testing among fathers)

6.2.2 Strengths and weaknesses

Strengths

Two key features of FUSAM make it stand out from routine TFP programme data:

The first strength is having information on long term outcomes, up to 2 years after the original admission date. Many programmes would miss late mortality so would overestimate their true public health impact.

The second strength is low losses to follow-up. Large numbers of unknown final outcomes can easily bias results. If the major reason for default is death, programme success would again be an overestimated. Another possible reason for default is that the child is better and the carer sees no reason to return for further follow-up: this pattern of defaulting would underestimate true cures. In FUSAM, we had long term outcome information on 899/1024 (88%) of children, but we also had baseline profile of those whose final outcome was unknown. For most variables, this was more similar to known survivors than to known deaths. This allows us to speculate that more unknowns survived than died and that our overall survival may be an underestimate.

Weaknesses

FUSAM is closely linked with PRONUT and relies on baseline data collected for the former. By the time funding was obtained and logistics organised for FUSAM, a large number of patients had already died. Resource limitations meant that when FUSAM finally started we were not able to revisit families of already known deaths. Additional FUSAM variables (e.g. starting and compliance with cotrimoxazole prophylaxis or ARV medications) were not thus available for all deaths. This missing data may have biased our findings on treatment and post-treatment factors associated with mortality. This is why the more complete baseline variables

rather than FUSAM-only variables were given prominence in the analysis and subject to more in-depth multivariable analysis.

It is critical to emphasise that FUSAM examined mortality risk factors for patients already enrolled in treatment. From a public health viewpoint it also important to know risk factors for all SAM patients in the population. This enables better decisions to be made about programme enrolment criteria. Whilst often plausible to assume that risk factor within programme are similar to those in the general population (e.g. HIV seropostivity; more severe wasting predicting higher risk of death), this cannot be taken as proven. Even if the risk factor itself is the same, the magnitudes of effect is likely to be different depending on the reference population.

Several of our variables relied on carer reports of symptoms experienced, family status and treatment received. This raises the possibility of reporting and recall bias. I suggest that systematic over or underreporting is unlikely given no consistent, strong associations between mortality and clinical status, family status and socioeconomic status. However, the increased 'noise' inherent to these more subjective, self-reported variables may have obscured small but real risks.

The last potential bias in our study related to seasonal variations in risk of malnutrition. Though recruitment was spread over most of a year and captured both rainy (hungry) season and dry (post-harvest) seasons, there may have been variations in nutritional status depending on what season a child was admitted and followed up in. Logistical constraints led to variations in time to follow-up. Had a constant time been possible, perhaps different magnitudes of z-score change might have been observed. I doubt however that the overall pattern of findings would have been significantly different. One of the advantages of using sibling controls was that they were measured at the same time as the ex-MOYO child. Where MOYO-sib differences are seen they cannot therefore be ascribed solely to seasonal variations.

6.2.3 Meaning of the study: generalizability

Generalizability is the key issue for many studies, and especially so for FUSAM:

i) Generalizability to other settings:

Whilst in many ways a typical resource poor developing country setting, MOYO had inputs and resources (in terms of staff time, clinical expertise, continuity of drug, food and equipment supplies) far above many TFPs in Malawi and elsewhere in Sub-Saharan Africa. For FUSAM, I believe that this strengthens rather than weakens the overall message that patient profile at admission (notably HIV status and severity of wasting) is the key risk factor for poor outcomes. If treatment had more of an impact on reducing mortality, then the effect of

admission profile would be attenuated and would not be so strongly correlated with mortality. One might also expect uptake of MOYO or post-MOYO interventions like ARVs, TB treatment, health education and SFP to have been more clearly related to mortality. If MOYO's treatments do not clearly make a great impact on outcomes, then most other treatment programmes are similarly unlikely to be able to do so.

ii) To CMAM therapeutic feeding programme

Despite its OTP component of care, MOYO is still fundamentally a traditional TFP. It is reactive in nature, admitting patients coming to the programme rather than going out to actively case find. This is different to CMAM programmes which actively seek patients with uncomplicated SAM in the community. The relative impact of pre-TFP status and TFP treatment may thus also be different.

iii) To feeding programmes which use WHO growth standards

MOYO recruited patients using NCHS-based case definitions of SAM and analysed z-scores using NCHS growth references. As outlined in the introduction **chapter 2.2.4**, new WHO growth standards are now increasingly being used. These label more children with SAM, and also suggest using an alternative % of weight gain discharge criterion. Again, all of this means that the risks and magnitude of risk cannot be directly extrapolated from FUSAM to a programme using WHO standards.

6.2.4 Comparison with other related studies

There are few other studies looking at long term outcomes following SAM. It is important therefore to briefly review the ones which are present in the literature. The striking issue with all of these is their age. Pre-HIV it is inevitable that most report better outcomes than FUSAM. Indeed, the best comparison may be between FUSAM's HIV negative patients and these studies:

- ***Niger, 1992***[113]

Of children 174 discharged from a TFP, 107(=61%) were followed up. At 3-16 months follow-up 17% had died. Though compared to FUSAM this appears better, there is clearly much larger probability of bias due to 39% unknowns, a proportion of whom will have been deaths.

- ***Zaire, 1987***[114]

In an endemic malnutrition area, 171 SAM children discharged from hospital were followed up and 81.6% found still alive at the end of 5 years. Similar to FUSAM, risk of death was highest in the first year following discharge.

- ***India, 1999***[115]

Discharged SAM children were compared to never malnourished siblings. Different to FUSAM, the ex-SAM children in this study had *better* wt/ht than their non-SAM sibs. The reason for the observation is uncertain and differs from FUSAM, which showed ex-SAM patients as more malnourished in the long term. Maybe in the Indian setting, the ex-SAM children were perceived as more vulnerable and therefore got preferential treatment/rations at home.

- **Tanzania, 1987**[116]

87% of 566 children who had been discharged from an NRU were followed over a year. The mortality after discharge was 8% and relapse rate was 13%. 75% were well, with good catch-up of wt/ht, but not ht/age. This mortality is clearly better than in FUSAM, but anthropometry findings consistent.

- **Guinea Bissau, 1995**[117]

In this retrospective cohort study, 1038 severely malnourished children (defined by weight-for-age <60% NCHS standards) were followed up over 3 years. 354 had received nutritional rehabilitation whereas 684 did not, due to limited programme capacity. Up to 3 years, the relative risk of death in the rehabilitated group was 0.75 (0.59 to 0.99). The mortality difference was greatest in the first three months. Weight-for-age z-scores improved from a baseline of -4.52 to -2.76. This is consistent with FUSAM's partial reversal of low weight-for-age.

6.2.5 Implications for policy and practice

There are four main messages and implications arising from FUSAM. Fortunately, all of these fit with rather than fight against current policy direction:

First, FUSAM suggests that similar TFP programmes (especially those in HIV prevalent settings such as sub-Saharan Africa) which only report short and medium term outcomes are

likely to be underestimating their mortality, and thus overestimating their true public health impact. A change of emphasis is urgently needed.

Second, FUSAMs risk factor profile implies that efforts to enrol patients at an earlier stage of SAM are likely to be beneficial. Such proactive approaches to care, consistent with CMAM-type nutrition programmes[9] are rapidly rolling out worldwide. FUSAM, rather than suggesting a change of direction is needed, reaffirms this existing direction. The results firmly imply that reactive programmes, which like MOYO do not use active case findings, should no longer be seen as an effective or acceptable approach to SAM.

Third, FUSAM is consistent with a push to earlier ARV therapy as a means of addressing high mortality amongst HIV positive children. It was striking that starting ARV treatment, compliance with ARV treatment and compliance with cotrimoxaxole did not seem to significantly reduce mortality in FUSAM's HIV positive population. One interpretation is that this treatment comes too late. Again, a more proactive approach diagnosing and treating HIV before SAM develops is likely to be important. Such early treatment is now recommended and many countries are rapidly scaling up access to HIV diagnostic and treatment services[52].

Fourth, a life course and more holistic approach is needed for SAM in general. Even with WHO growth standards effectively enrolling a larger and less severely wasted group of children, more proactive approaches are needed to address SAM *before* it develops. Such primary prevention strategies could include treatment of MAM but also treating the wider social and economic circumstances which give rise to malnutrition in the first place. Whilst these social factors were not independently associated with mortality risk (adjusting for admission anthropometry) in our study, they are linked to risk of low weight-for-height. An important observation is that in the year following FUSAM, there were less admissions to MOYO than seen for many years. This was not obviously due to CMAM (which was only just rolling out) but, probably, due to a very successful fertilizer subsidy programme which the government had introduced in an attempt to improve crop yield for the poorest smallholder farmers in the community.

6.2.6 *Unanswered questions and future research*

FUSAM raises many questions for future research.

One which could relatively easily and quickly be answered is whether community case finding and early enrolment of SAM patients to treatment improves their long term outcomes. The case for improved short term outcomes in CMAM programmes has already been forcefully made[2],[34] – albeit without any evidence from gold standard randomised controlled trials. Long term follow-up of ex-CMAM patients is needed to determine whether their outcomes are, as I would expect, indeed better than from a MOYO-type programme.

Long term follow-up of patients from programmes using WHO growth standards is also needed. One key difference to NCHS is that discharge is now recommended using a % weight gain criterion rather than a target weight as before. There could be potential problems with this. Notably that patients who are extremely malnourished at baseline would still be relatively wasted at discharge even having gained their 15-20% weight.

Research is needed as to optimal timing of ARVs. Could ARVs earlier in a TFP lead to the same benefits as ARVs pre-SAM? Or is the latter the only way to make significant impact on HIV-related mortality?

More emphasis is needed into primary prevention of malnutrition. Not just for SAM but for all forms of malnutrition, notably stunting. It is especially disappointing that stunting was largely unaffected even in otherwise successful MOYO treatment. Related evidence from a classic *Pediatrics* paper[118] suggests that impact on child malnutrition needs not just early but even prenatal intervention if the immediate onset of stunting is to be avoided:

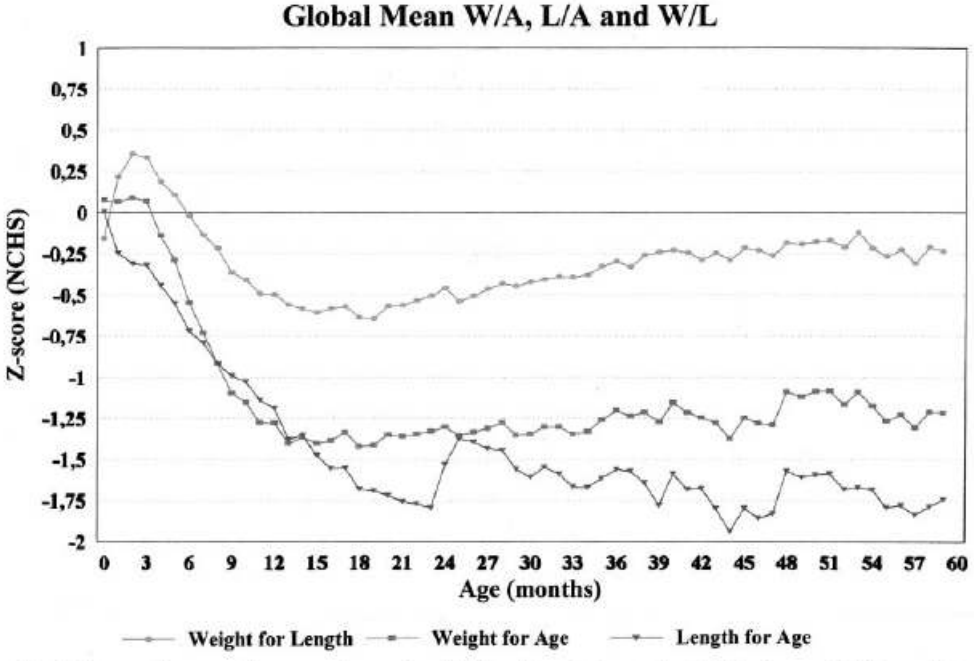


Fig 1. Mean anthropometric z scores by age for all 39 studies, relative to the NCHS reference (0–59 months).

Figure 32 Onset of stunting, wasting and underweight (Shrimpton et al, Pediatrics, 2001)

More work is needed on how to optimise outcomes for those who do slip through the primary prevention nets. What is it about some children in a family that they become severely malnourished whereas others do not? Which interventions, targeted at which SAM subgroup, would have most impact minimising the SAM-related mortality and morbidity risks described in this thesis? Recognizing the particularly high mortality in MOYO, could any interventions make additional reductions in death there (e.g. stricter implementation of the "10 Steps" guidelines; a modified feeding protocol; a modified feed)

Finally, as a general principle, I would urge for any future studies to be interventional rather than just observational in design. As I hope that PRONUT and FUSAM have demonstrated, observational trials can take advantage of and indeed link rather neatly to intervention projects. They provide useful background data to help formulate the *next* intervention(s). As PRONUT also demonstrated, what is plausible and promising in theory does not always work as expected (if at all!) in practice. Children with SAM need and deserve the best possible programmes and policies. These must be both effective and cost-effective The best possible programmes and policies are those which are robustly evidence-based. This means gold-standard randomized controlled trials wherever possible.

Chapter 7

CONCLUSIONS

Acute malnutrition and in particular outpatient-focused CMAM strategies are currently high on the international child health and nutrition policy agenda[9]. It is important to capitalise on this and build two concluding messages and implications arising from PRONUT and FUSAM:

1) In PRONUT, addition of a functional food, Synbiotic2000 Forte™, to standard RUTF did not improve outcomes. Explanations other than no effect include deaths from causes unaffected by Synbiotic actions; organism sensitivity to cotrimoxazole antibiotics; Synbiotic sharing or cross-infection between children; suboptimal dose/dose regime.

The observation of reduced outpatient mortality may be due to bias, confounding or chance, but is biologically plausible, and could be explored in future studies using different functional foods. It is relevant not just to SAM but to MAM and other less acute forms of malnutrition. It would be especially relevant if the recently resurrected hypothesis of enteropathy-associated malnutrition accounts for more malnutrition than recognised by current treatment strategies[111].

2) Given the overall negative findings of PRONUT and the risk factors identified in FUSAM, it is more promising in the short term to pursue high quality, high coverage rollout of existing interventions. It is important to treat both SAM and HIV as early as possible. Community-based CMAM-type strategies are likely to play a key role identifying and treating high risk patients as well as proving long term support to those discharged from treatment.

Opportunities for future research on SAM should be taken. These should focus on community based strategies and should include work on primary prevention of SAM. The potential to make a difference to 13 million SAM-affected children and over 1 million SAM-related deaths has never been better.

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APPENDICES

Annex A. Research articles – summary list

A.1 Directly related to thesis

2009

i. Bunn J, Thindwa M, **Kerac M**. Features associated with underlying HIV infection in severe acute childhood malnutrition: a cross sectional study. ***Malawi Medical Journal*** 2009 Vol 21, Issue 3, p 108 http://www.mmj.medcol.mw/issues/vol21_3malnutrition.pdf

ii. **Kerac M,** Bunn J, Seal A, Thindwa M, Tomkins T, Sadler K, Bahwere P, Collins S. Treatment of Severe Acute Malnutrition (SAM) using probiotic/prebiotic-enhanced therapeutic food in a HIV prevalent setting: A double-blind efficacy RCT in Malawi(The "PRONUT study" ~ PRObiotics in malNUTrition) – ***The Lancet****, Vol 374, Issue 9684, p 136 to 144, 11th July 2009.* doi:10.1016/S0140-6736(09)60884-9 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)60884-9/abstract

iii. **Kerac M**, Seal A, Blencowe H, Bunn J. Improved Assessment of child nutritional status using target weights and a novel low-cost weight-for-height slide chart. ***Tropical Doctor*** 39(1): 23-26; doi:10.1258/td.2008.080096. http://td.rsmjournals.com/cgi/content/full/39/1/23

A.2 Related to theme of Severe Acute Malnutrition

2009

i. **Kerac M**, Blencowe H, Grijalva Eternod C, McGrath M, Shoham J, Seal A. Prevalence of wasting in infants aged <6 months and implications of 2006 WHO Child Growth Standards for selective feeding programmes in nutritionally vulnerable settings. ***(in press, ADC, accepted December 2010)***

ii. Fergusson P, Tomkins A, **Kerac M**. Improving the management of Severe Acute Malnutrition in HIV prevalent settings. ***International Health (Review)*** *Vol 1, Issue 1, Sept 2009, p 10-16.* doi:10.1016/j.inhe.2009.03.001 *http://download.journals.elsevierhealth.com/pdfs/journals/18763413/PIIS187634130900007.pdf*

iii. **Kerac, M**; Egan R; Mayer, S; Walsh A; Seal A. New WHO Growth Standards: rollout needs more resources. ***The Lancet (Commentary)****, Vol 374, Issue 9684, p 100 to 101, 11th July 2009.* doi:10.1016/S0140-6736(09)61266-6 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61264-2/fulltext

iv. Skordis-Worrall, J & **Kerac, M**. Localized or centralized control of food production for treating severe acute malnutrition: echoes of a past child survival revolution? ***Maternal and Child Nutrition (Editorial),*** *Vol 5(3) 195-198* *http://www3.interscience.wiley.com/journal/122456010/abstract*

2008

v. Thurstans S, **Kerac M**, Maleta K, Banda T, Nesbitt A. HIV prevalence in severely malnourished children admitted to nutrition rehabilitation units in Malawi: Geographical & seasonal variations, a cross sectional study. ***BMC Paediatrics*** 2008, **8**:22 doi:10.1186/1471-2431-8-22 http://www.biomedcentral.com/1471-2431/8/22 (published online 21st May 2008)

vi. Sadler K, **Kerac M**, Collins S, Khengere H, Nesbitt A, Improving the Management of Severe Acute Malnutrition in an Area of High HIV Prevalence, ***Journal of Tropical Pediatrics*****.** doi: 10.1093/tropej/fmn029 (published online May 1st 2008) http://tropej.oxfordjournals.org/cgi/content/abstract/54/6/364

2007

vii. Seal A & **Kerac M.** 'Operational implications of the use of the 2006 WHO Growth Standards in nutrition programmes: secondary data analysis. ***British Medical Journal*****,** doi:10.1136/bmj.39101.664109.AE (publ. online 23 February 2007) http://www.bmj.com/cgi/content/abstract/334/7596/733
+ response to letter on paper, ***BMJ online rapid responses*** http://www.bmj.com/cgi/eletters/334/7596/733

viii. **Kerac M &** Seal A, 'The new 2006 WHO Growth standards: What will they mean for emergency nutrition programmes?' ***Field Exchange (commentary)***, 2006; 28:15-6 (http://www.ennonline.net/fex/current/Fex28.pdf)

Annex B. Presentations to meetings – summary

B.1 Policy & General meetings (directly & indirectly PhD-related)

2009

i. SPHERE (Humanitarian Charter & Minimum Standards in Disaster Response), 2010 update meeting

Core working group for nutrition *Save the Children UK, London, October 22th to 23rd 2009*

International consultative meeting for the revision of the nutrition components of the Sphere Handbook,

ii. Global Nutrition Cluster Annual Meeting

Bonhill House, London UK, October 20th to 21st 2009

- Presented summary of MAMI (Management of Acute Malnutrition in Infants) project

http://oneresponse.info/GlobalClusters/Nutrition/Documents/GNC%20Annual%20Meeting%20Report%2020-21%20October%202009.pdf

http://oneresponse.info/GlobalClusters/Nutrition/Pages/Global%20Cluster%20Meetings.aspx

iii. SPHERE (Humanitarian Charter & Minimum Standards in Disaster Response), 2010 update meeting

Mt Soche Hotel, Blantyre, Malawi, August 10th to 11th 2009

Malawi consultative meeting for the revision of the nutrition components of the Sphere Handbook,

- Presentation on implications of new WHO-Growth standards & latest evidence regarding infants <6months

2007 & before

iv. World Bank (International) Development Marketplace 2007 (Health, Population & Nutrition),

World Bank, Washington DC, USA. May 21st to 23rd 2007

Poster presentation (finalist project, last 104 / 2800 original applications worldwide):

~ "Community-Therapeutic Care – New Generation" Development of a new, cost-effective therapeutic food for severely malnourished children

http://siteresources.worldbank.org/DEVMARKETPLACE/Resources/finalistsbook.final.pdf *(page 13)*

v. National CTC Review Workshop,

Malawi Institute of Management, Lilongwe, Malawi**,** April 19th 2006

Lecture presentation (Marko Kerac, representing co-authors: Sadler K, **Kerac M**, Collins S, Khengere H, Nesbitt A)

~ "CTC experience and protocols, MOYO house, QECH, Blantyre"

B.2 Academic Meetings (directly and indirectly related to PhD)

2009

vi. MAINN (Maternal & Infant Nutrition & Nurture) Conference

University of Lancashire, UK, September 7th 2009

Workshop presentation:(led by Marko Kerac)

Kerac M, McGrath M, Bizouerne C, Wilkinson C, Shoham J, Seal A MAMI (Management of Acute Malnutrition in Infants). A review of current field management of acutely malnourished infants under six months of age

vii. CAPGAN (Commonwealth Association of Paediatric Gastroenterology & Nutrition)

Blantyre, Malawi, August 12th to 16th 2009

http://www.mmj.medcol.mw/issues/vol21_3abstracts.pdf

Accepted for oral presentation

- ***Marko Kerac presented:***

1) Probiotic/prebiotic-enhanced therapeutic food for treatment of severe acute malnutrition in an HIV prevalent setting: a double-blind efficacy RCT in Malawi. **M.Kerac**, J.Bunn A.Seal, M.Thindwa, A.Tomkins, K.Sadler,P.Bahwere, S.Collins

2) Child growth standards for child health & nutrition programmes treating wasted infants aged <6 months: secondary data analysis of 21 DHS datasets. **M.Kerac**, M.McGrath, C.Grijalva-eternod, H.Blencowe, J.Shoham, A.Seal

- ***Co-author presented (presenting author underlined)***

3) Long-term follow-up of children treated for severe acute Malnutrition: a longitudinal cohort study. **M.Kerac**, G Chagaluka, S Collins, P Bahwere, R Mathisen, S Chitekwe, J Bunn.

4) Mortality a year after admission with HIV and severe acute Malnutrition in Malawi: a cohort study. J. Bunn, G.Chagaluka, **M.Kerac**

5) A review of bacterial infections in malnourished infants aged under 6 months: implications for Case management in developing countries. H.Bailey, **M.Kerac**, A.Seal.

6) Modification of the Prudhon index for HIV prevalent settings. J.Bunn, V.Nyirongo, **M.Kerac**

- ***Accepted for poster presentation (author underlined presented)***

7) Evaluating the Moyo chart – a novel, low-cost, weight-for-height slide chart for improved assessment of nutritional status in children. C.Sikorski, **M.Kerac,** M.Fikremariam, A.Seal.

8) Routine antibiotics for uncomplicated & complicated severe acute malnutrition in children aged 6-59 months: a review of the evidence base underyling current practice. G.Alcoba-Wright, **M.Kerac**

viii. MSF (Medecins Sans Frontiers) Scientific Day

London, UK, June 11th 2009 *http://www.msf.org.uk/sciday09.event*

Co-author of lecture presentation *(presented by Carlos Grijalva-Eternod, representing co-authors* Grijalva- Eternod C; Kerac M; Blencowe H, McGrath M; Shoham J; Seal*)*

~ "Wasting in infants < 6 months: prevalence and implications for emergency feeding programmes of the 2006 WHO Child Growth Standards"

ix. Royal College of Paediatrics & Child Health Spring Meeting (International Health / VSO section)

York, UK, April 1st 2009

http://ichg.org.uk/publications/CHILD2015_Global_Communications_Package_ICHG_VSO_RCPCH_2009.pdf

a) Lecture presentation (Dr Marko Kerac, representing co-authors: Blencowe H; Kerac M; McGrath M; Grijalva-Eternod C; Shoham J; Seal A)

~ "Disease burden and risk-benefit implications of using new WHO Child Growth Standards to diagnose Severe Acute Malnutrition in infants <6 months age: Secondary data analysis of 21 developing country DHS surveys"

b) Co-author of lecture presentation (presented by Dr Hannah Blencowe, representing co-authors: Blencowe H; **Kerac M**; Molyneux E)

~ "'Task-shifting' to reduce neonatal mortality in a tertiary referral hospital in a developing country"

x. UCL Research Student's poster day –

UCL, London, UK, March 6th 2009

Poster presentation (presented by Dr Marko Kerac, representing co-authors: **Kerac M**; Blencowe H; McGrath M; Grijalva-Eternod C; Seal A)

~ "Acute Malnutrition in <6 month old infants: Developing country disease burden & implications of the new WHO Child Growth Standards"

2008

xi. Royal Society of Tropical Medicine & Hygiene "Research in Progress" day

SOAS, London, UK, December 18th 2008

Two poster presentations: *(presented by Marko Kerac, representing co-authors listed)*

a). "PRONUT" Study ~ A double blind randomised controlled trial to evaluate the efficacy of pre/probiotic enhanced Ready-to-Use Therapeutic Food (RUTF) in the treatment of severe acute childhood malnutrition. **Kerac M**; Bunn J; Seal A; Thindwa M; Bahwere P; Sadler K; Tomkins A; Collins S

b) "Acute Malnutrition in <6 month old infants: Developing country disease burden & implications of the new WHO Child Growth Standards" Blencowe H**, Kerac M**, McGrath M, Grijalva-Eternod C, Seal A

xii. Institute of Child Health Research Students' poster day –

ICH, London, UK, November 26th 2008

Poster preparation (presented by Dr Andrew Seal, representing co-authors: **Kerac M**, Blencowe H, McGrath M, Grijalva-Eternod C, Seal A)

~ "Acute Malnutrition in <6 month old infants: Developing country disease burden & implications of the new WHO Child Growth Standards"

2007

xiii. Institute of Child Health Research Students' poster Day

ICH, London, UK, November 28th 2007

Poster preparation (presented by Dr Andrew Seal, representing co-authors: **Kerac M**; Bunn J; Seal A; Thindwa M; Bahwere P; Sadler K; Tomkins A; Collins S)

~ *"PRONUT" Study* ~ A double blind randomised controlled trial to evaluate the efficacy of pre/probiotic enhanced Ready-to-Use Therapeutic Food (RUTF) in the treatment of severe acute childhood malnutrition

xiv. 11th COMREC National Research & Dissemination Conference,

College of Medicine, Blantyre, Malawi, November 24th 2007 http://www.medcol.mw/com/Program.pdf

Lecture presentation (Marko Kerac, representing co-authors: **Kerac M**; Bunn J; Seal A; Thindwa M; Bahwere P; Sadler K; Tomkins A; Collins S)

~ *"PRONUT" Study* ~ A double blind randomised controlled trial to evaluate the efficacy of pre/probiotic enhanced Ready-to-Use Therapeutic Food (RUTF) in the treatment of severe acute childhood malnutrition

xv. International Policy & Research Planning Workshop: Blantyre Technical Review ~ Improving the Management of Severely Malnourished Children with HIV in Sub-Saharan African,

Queen Elizabeth Central Hospital, Blantyre, Malawi, January 28th-30th 2007

Three lecture presentations (Marko Kerac, representing co-authors)

a) *"Increasing therapeutic feeding programme capacity by offering RUTF in place of F100"*: **Kerac M**, Lim J, Bunn J.

b) *"Potential use & effect of probiotics in severely malnourished Malawian children"* **Kerac M**

c) *"Data handling, data quality & longitudinal analysis"* **Kerac M**

xvi. 2nd Malawi Annual HIV Nutrition Meeting,

College of Medicine, Blantyre, Malawi, Jan 27th 2007

Lecture presentation (Marko Kerac, representing co-authors (**Kerac M**, Bunn J)

~ *"Excess mortality risk associated with HIV infection in a large Malawian NRU"*

2006 and before

xvii. 10th COMREC (College of Medicine Research & Ethics Committee) National Research & Dissemination Conference,

College of Medicine, Blantyre, Malawi, November 11th 2006

Lecture presentation (Marko Kerac, representing co-authors: Thurstans S, **Kerac M**, Maleta K, Banda T, Nesbitt A)

~ *"HIV Prevalence in Malawian NRUs"*

Annex C. Ethical approvals and patient consent forms

C.1 PRONUT ethical approval

C.1.1 Original

UNIVERSITY OF MALAWI

Principal

Prof. R.L. Broadhead, MBBS, FRCP, FRCPCH,DCH

Our Ref.: MC/COMREC/16

College of Medicine
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Chichiri
Blarityre 3
Malawi
Telephone: 01 671 911/01 674377
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31 st January, 2005

Dr S. Collins
C/o Concern Worldwide
P.O Box 1747 Lilongwe

Dear Dr Collins,

P.O3/04/236 -A study to compare the efficacy of three formulations of readv-to-use therapeutic foods in the treatment of severe acute malnutrition

I write to inform you that COMREC reviewed and approved the progress report which you submitted. I am pleased to inform you that COMREC approved the continuation of the study for another 12 months with effect from 1 st January, 2005.

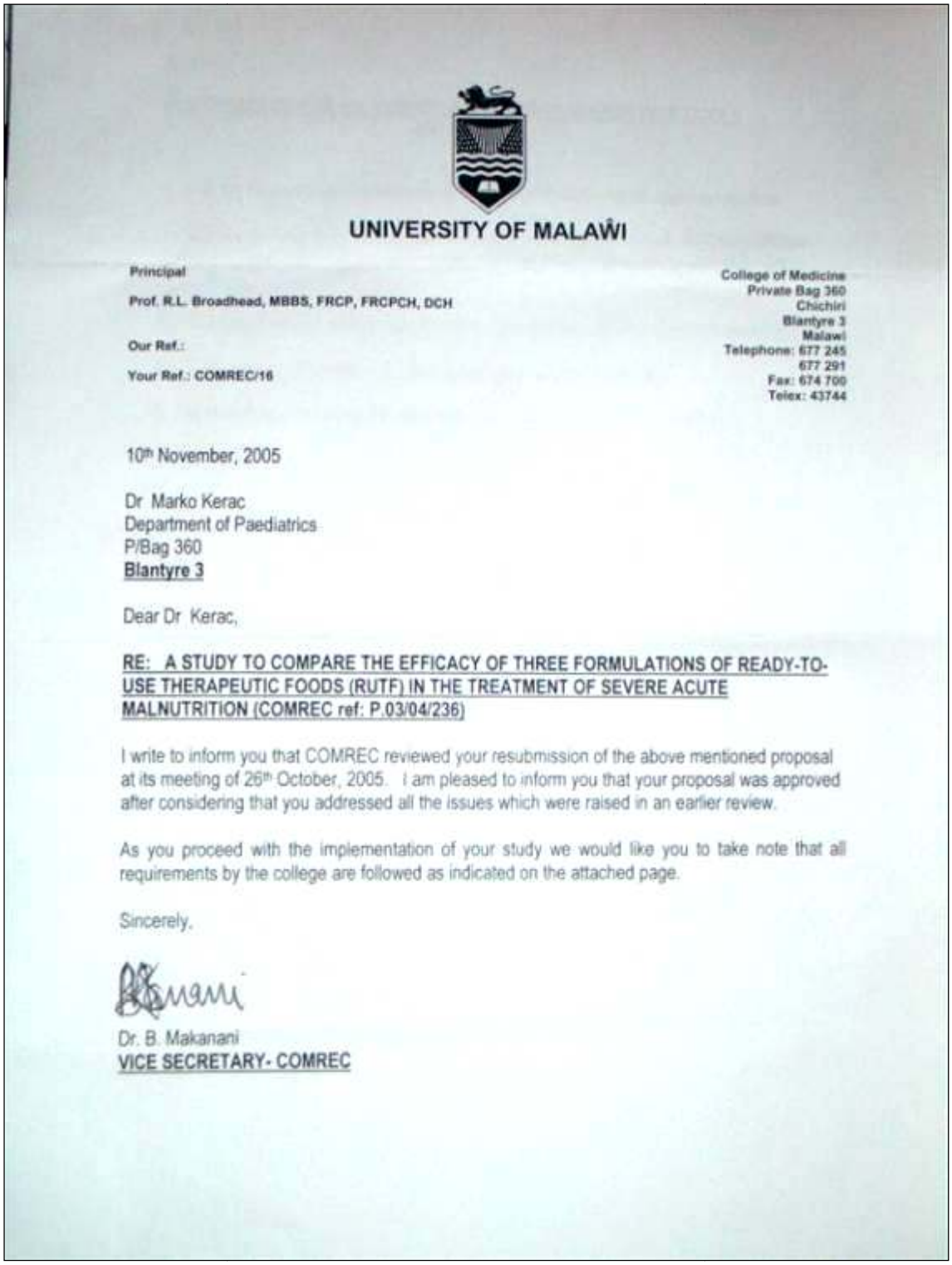
However, on the issue of change of site, the committee would like you to send documentation as proof of your permission to conduct the project at Umoyo Rehabilitaion at QECH.

This renewal is subject to continued adherence to the College of Medicine requirements for all COMREC approved research studies.

Yours sincerely,

Dr .I. Kumwenda
CHAIRMAN -COMREC

C.1.2 Update



UNIVERSITY OF MALAWI

Principal

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10th November, 2005

Dr Marko Kerac
Department of Paediatrics
P/Bag 360
Blantyre 3

Dear Dr Kerac,

RE: A STUDY TO COMPARE THE EFFICACY OF THREE FORMULATIONS OF READY-TO-USE THERAPEUTIC FOODS (RUTF) IN THE TREATMENT OF SEVERE ACUTE MALNUTRITION (COMREC ref: P.03/04/236)

I write to inform you that COMREC reviewed your resubmission of the above mentioned proposal at its meeting of 26th October, 2005. I am pleased to inform you that your proposal was approved after considering that you addressed all the issues which were raised in an earlier review.

As you proceed with the implementation of your study we would like you to take note that all requirements by the college are followed as indicated on the attached page.

Sincerely,

Dr. B. Makanani
VICE SECRETARY- COMREC

C.2 Informed voluntary consent form (English)

MOYO 'PRONUT' STUDY
~ INFORMED VOLUNTARY CONSENT FORM~

PLEASE KEEP THIS FOR YOUR INFORMATION

PLEASE SHOW THIS TO YOUR HEALTH CARE PROFESSIONAL
IF SEEKING TREATMENT OUTSIDE OF MOYO DURING THE COURSE OF THE STUDY:
Any health professional should administer appropriate initial treatment and then refer the child back to Moyo as soon as possible. Thank you for your cooperation.

I understand that:

- ✓ My child is suffering from severe acute malnutrition. This condition is frequently associated with diarrhoea. The current standard treatment includes a routine antibiotic treatment and for nutritional rehabilitation a therapeutic milk during the stabilization phase and local made Plumpy'nut during outpatient care. In most cases, successful recovery occurs in 4 weeks.
- ✓ This research is carried out to find improved and sustainable methods of treatment of severe acute malnutrition. In view of this, a new formulation of RUTF is being compared to local made Plumpy'nut:
  - This new recipe is locally made Plumpy'nut with the addition of a mixture of probiotic and prebiotics called Synbiotic 2000 forte® (Medipharm AB, Kågeröd, Sweden). Recent results from prospective controlled trials in post operative patients suggest that combinations of pre- and probiotics, referred to as 'synbiotics' can reduce greatly the incidence of post operative infection, shorten recovery times and reduce the need for antibiotics. Synbiotic 2000 contains probiotic bacteria that are normally present in the gut and have been used in human trials without any adverse effects.
  - Probiotics are organisms similar to those found in eating yogurt. Very rarely they can cause infection. If my child develops fever or other adverse reactions, I will return as soon as possible to the ward where I will receive appropriate treatment.
- ✓ The potential benefits to the target population are quicker recovery, reduced incidence of diarrhea and other illnesses, and therefore better treatment of both severely and moderately malnourished children.
- ✓ Confidentiality of each study participant will be maintained at all times through the allocation of a unique identification number.

If you are volunteer to participate in the trial you should expect the following:

1. Your child will be admitted in the nutrition programme for treatment of acute severe malnutrition until reaching the discharge criteria.
2. After admission, when your child is ready for solid foods, he/she will be given one of the 2 formulations of RUTF (1 experimental and the local made Plumpy'nut).
3. If you do not participate in the trial, you will not be denied treatment.
4. You have the right to withdraw from the study after initial enrollment.
5. Contact details for the study team are below, in order that response to queries can be as quick and efficient as possible:

Dr Marko Kerac, LEAD INVESTIGATOR
c/o MOYO HOUSE Nutritional Rehabilitation Unit, Queen Elizabeth Hospital, Chipatala Avenue, Blantyre
(Post: c/o Department Paediatrics, P/Bag 360, Blantyre 3) (Tel: 01 874 333; 01 877 333; 01 875 694)

Minimising Risks:

Your malnourished child will be evaluated by trained personnel on presentation to a health centre or NRU. He will be included in the study if he is suffering from uncomplicated severe acute malnutrition. If he is suffering from complicated severe acute malnutrition, he will be treated for the complications according to the standard protocol and be included in the study when he has improved and is ready to eat RUTF.

Your malnourished child will be closely monitored by the study team through out the study. In the exceptional case of your child showing any adverse reaction to the nutritional treatment prescribed we will immediately withdraw your child from the study, return your child to standard nutritional treatment and will treat, to the best of our ability, the adverse reactions presented.

If you agree to participate, please sign your name below or give your left thumb impression. Thank you.

Signature of Patient …….. Signature of Investigator …….

Date..... **Date.....**

C.3 Informed voluntary consent form (Chichewa)

MOYO 'PRONUT' STUDY
~ FOMU YOVOMEREZA ~

CHONDE SAMALANI BWINO FOMUYI

CHIKALATACHI NDIPO KUMBUKIRANI KUYITENGA NDIKUYIWONETSA KWA DOTOLO PAMENE MUKUPITA KUKALANDIRA CHITHANDIZO KU ZIPATALA ZINA PA NYENGO YONSE YA IMENE MULI MUKAFUKUFUKUYU

Kwa onse ogwira ntchito ya chipatala: chonde mutitumizire mwanayo kuno ku MOYO HOUSE mutatha kumupatsa chitandizo choyambilira. Zikomo.

NDIVOMEREZA KUTI:

~ Mwana wanga akuperewera zakudya zoyenera za magulu, mthupi mwake. Ndipo kutsegula m'mimba kumadza pafupi pafupi chifukwa chavutoli. Matendawa amagonjetsedwa pakumwa mankhwala opha tizilombo m'mimba mwa mwanayo ndipo kupereweredwa kwa zakudya kumagonjetsedwa ndi mkaka wokhala ndi zakudya zomanga ndi kulimbitsa thupi nthawi imene agonekedwa ku chipatala komanso mwanayo akaonetsa kusintha, amapatsidwa chiponde cha mtedza pamasiku amene akuyendera ku chipatala kuchokera kunyumba. Pa ma sabata anayi, mwanayo amasonyeza kusintha kusonyeza moyo wathanzi ndithu.

~ Kafukufukuyu akuchitika ndi cholinga choti papezeke njira zabwino zokhalitsa zogonjetsera kupereweredwa kwa zakudya mthupi mwa mwana. Pachifukwa ichi, chiponde chapangidwanso china chatsopano (chopangidwada kwathu konkuno):

- Mtundu wa chakudya chimenechi ndicho chiponde cha mtedza, mkaka, sugar chosakanizidwa ndi synbiotic 2000 forte (ndipo muli zipangizo zina zokhala ngati zamu yogati). Mankhwala a synbiotic 2000 forte (medipharm AB, kagerod,Sweden) ayesedwa ndipo zotsatira zake zaonetsa kuti odwala sangapitilirenso kugwidwa ndimatenda otsekula m'mimba kapena kuchepekedwa zakudya mthupi, komanso zimathandiza munthu kuchira msanga. Ndipo mankhwala ena ophera tizilombo toyambitsa matenda mthupi saliofunika pafupipafupi. Synbiotic 2000 forte anayesedwa kuwanthu popanda chokhumudwitsa chirichonse.
- Probiotics ndi tizirombo tofanana ndi tomwe timapezeka mu Chakudya ngati Yogati, tomwe timayambitsa matenda mu ana ochepa kwambiri monga kutentha thupi koma kawiri kawiri sitiyambitsa matenda. Ngati mwana wanga atenda thupi, kapena mavuto ena, ndidzabwelera naye mwansanga ku Chipatala kumene ndikalandire chithandizo choyenera.

~ Phindu lake kwa ofunika kupatsidwa chakudyachi likuyembekezeka kukhala: kuchira mofulumira, kuchepetsa matenda otsegula m'mimba ndi matenda ena, komanso kuchiza matenda a kusowa kwa zakudya mthupi.

~ Chinsisi cha mwana aliyense wolandila chithandizo cha zakudya za chiponde (chakudya chokonzeratu chobwezera thanzi mthupi chopatsidwa kwa anthu amatupi onyentchera chifukwa chamatenda) chidzasungidwa bwino lomwe posalemba dzina la mwanano m'malo mwake aliyense adzapatsidwa nambala ngati chizindikiro chake.

NGATI MWADZIPEREKA KUTHANDIZA NAWO PA KAFUKUFUKUYU, MUVOMEREZE KUTI:

1. Mwana wanu adzagonekedwa ku chipatala pa ndondomeko yolandira chakudya chamagulu komanso chakudya cha mankhwala othetsa kusowa kwa zakudya mthupi mpaka nthawi imene adzapezere bwino ndikutuluka mchipatala.
2. Pamena mwana wanu agonekedwa kuchipatala adzapatsidwa chimodzi mwa zakudya za mitundu iwiri ya RUTF (chiponde); choyamba chosakaniza mankhwala a synbiotic 2000 forte; chachiwiri chopanda mankhwala.(pamene mwana wayamba kupeza bwino)
3. Ngakhale musalowe nawo mu kaundula wakafukufukuyu, muli ololedwa kulandila mankhwala ndi chithandizo.
4. Simulioumilizidwa kukhalamo mkaundula wakafukufuku mukhoza kutulukamo nthawi ina iri yonse.
5. Ngati muli ndi mafunso mukhoza kufunsa kwa:

Dr Marko Kerac, LEAD INVESTIGATOR
c/o MOYO HOUSE Nutritional Rehabilitation Unit, Queen Elizabeth Hospital, Chipatala Avenue, Blantyre
(Post: c/o Department Paediatrics, P/Bag 360, Blantyre 3) (Tel: 01 874 333; 01 877 333; 01 875 694)

CHITETEZO

Mwana wanu adzayesedwa ndipo adzalowa nawo mkaundula wa kafukufuku wa matenda osowa zakudya mnthupi. Adzapatsidwa chakudya chamankhwala ndiponso chamagulu ndipo adzalembedwa mu kafukufuku pamene mwanayo wayamba kupeza bwino.

Mwana wanu adzaonedwa pafupi pafupi ndi anthu omwe akonza kafukufukuyu panyengo yonse mwanayo adzakhala ku chipatala. Ngati mwana wanu adzasonyeza kusagwirizana ndi zakudya zamankhwalazo, adzaimitsidwa ndikuchotsedwa mukawundula wakafukufukuyo, ndipo adzaperekedwa ku ndondomeko ya zakudya zamagulu kuti alandile chithandizo choyenera kufikira achire ndithu.

Ngati muvomereza ndi kugwirizana nazo zonse zalembedwazi, chonde lembani dzina lanu pamusipa kapena kusindikiza chala chanu. Zikomo

PROJECT IYI YAPANGIDWA APURUVU NDI 'COMREC' (College of Medicine Research & Ethics Committee), ref. P03/04/236

C.4 FUSAM ethical approval form

UNIVERSITY OF MALAŴI

Principal

Prof. R.L. Broadhead, MBBS, FRCP, FRCPCH, DCH

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4th February, 2008

Dr M. Kerac
Paediatrics Department
P/Bag 360
Blantyre 3

Dear Dr Kerac,

P.03/04/236 –A study to compare the efficacy of three formulation of ready-to-use therapeutic foods (RUTF) in the treatment of severe acute malnutrition

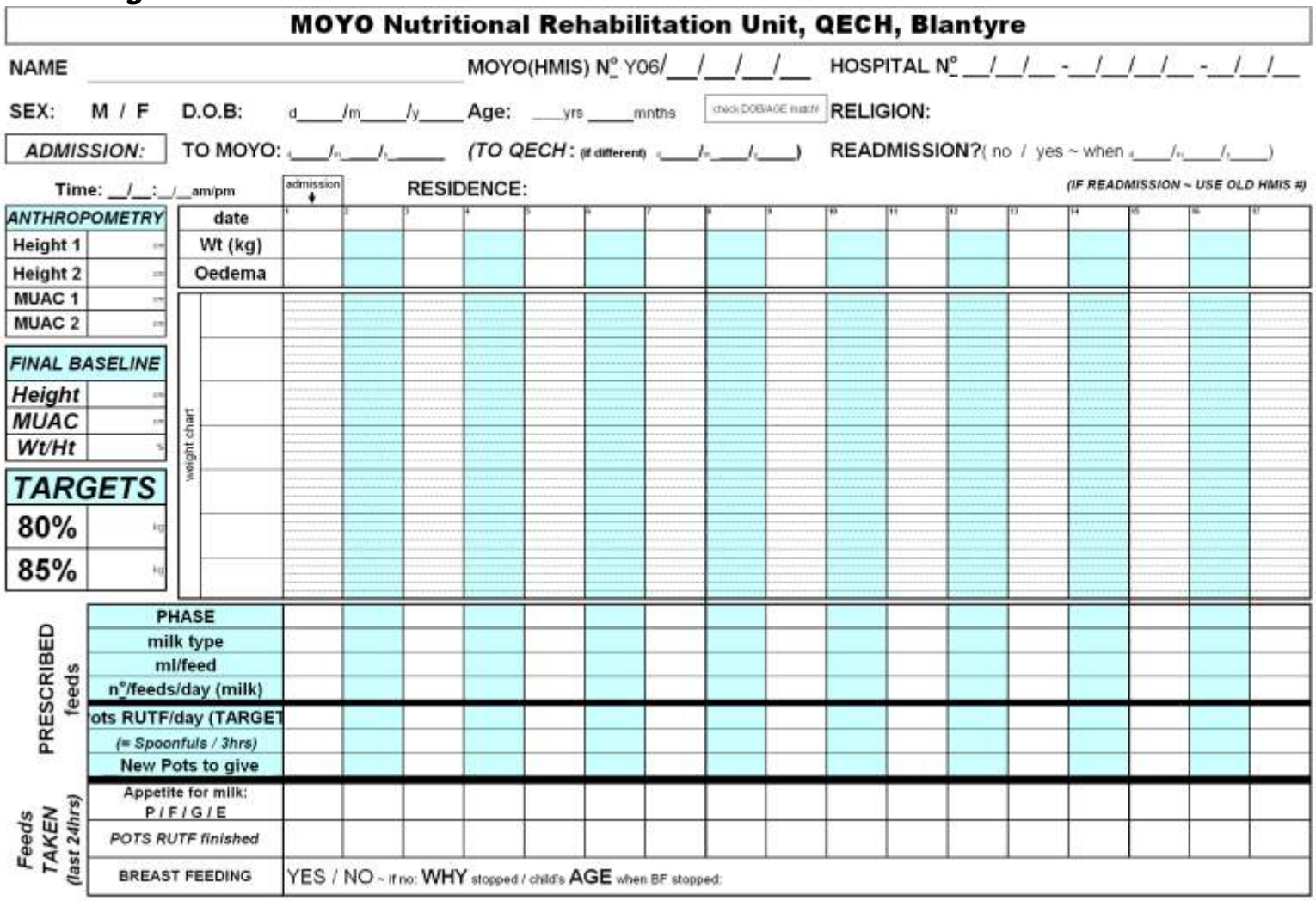
I write to inform you that COMREC reviewed your revised expansion for follow up of the above research project which you resubmitted. I am pleased to inform you that your request for expansion has been approved.

Yours sincerely,

Prof. J.M. Mfutso Bengo
SECRETARY - COMREC

Annex D. MOYO Ward forms and protocols

D.1 Weight chart



MOYO Nutritional Rehabilitation Unit, QECH, Blantyre

NAME _____ MOYO(HMIS) N° Y06/__/__/__/__ HOSPITAL N° __/__/__ - __/__/__/__ - __/__/__

SEX: M / F D.O.B: d____/m____/y____ Age: ___yrs ____mnths check DOB/AGE match RELIGION:

ADMISSION: TO MOYO: d____/m____/y____ (TO QECH: (if different) d____/m____/y____) READMISSION? (no / yes ~ when d____/m____/y____)

Time: __/__:__/__am/pm admission RESIDENCE: (IF READMISSION ~ USE OLD HMIS #)

ANTHROPOMETRY	
Height 1	cm
Height 2	cm
MUAC 1	cm
MUAC 2	cm

FINAL BASELINE	
Height	cm
MUAC	cm
Wt/Ht	%

TARGETS	
80%	kg
85%	kg

	date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	Wt (kg)																	
	Oedema																	
weight chart																		

PRESCRIBED feeds																		
	PHASE																	
	milk type																	
	ml/feed																	
	n°/feeds/day (milk)																	
	ots RUTF/day (TARGET																	
	(= Spoonfuls / 3hrs)																	
	New Pots to give																	
Feeds TAKEN (last 24hrs)	Appetite for milk: P / F / G / E																	
	POTS RUTF finished																	
	BREAST FEEDING	YES / NO ~ if no: WHY stopped / child's AGE when BF stopped:																

D.2 Drug and inpatient symptom chart

MOYO ~ DRUG CHART & CCP Name_____ D.O.B d___ /m____ /y___ MOYO (HMIS) number: Y06/___/___/___/___ **p. 1**

Admission Wt:		Date:				MOYO ~ WEEK 1							MOYO ~ WEEK 2			
						admission	2	3	4	5	6	7	8	9	10	11
TIME drugs given																
DRUGS:	dose	freq.	via	days	date =>changes	please sign when drug has been given										
Folic acid	5 mg	d. 1	po	1 dose												
Vitamin A	200,000iu	d. 1&2	po	/	NIL if given recently REDUCE dose if <1yr											
Albendazole	200mg/ 400mg	stat	po	1 dose	nil if <1 yr; 400g if >2yrs											
Co-trimoxazole	120/240mg	bd	po	10												
GV mouthwash / nystatin oral drops		QDS	po		*AFTER Feeds*											
FLUIDS	IVI / Tx / Resomal (PRN, reg)															
O2 / NGT	(note if present)															
CLINICAL (Hx, Ex)																
Progress	Worse (⇩) / Same (⇔) / Better (⇧)															
Stool	(N)ormal / (L)oose / (W)atery / (B)loody															
frequency	TODAY (since sunrise) / 24 HRS (sunrise YEST. to sunrise today)					/	/	/	/	/	/	/	/	/	/	/
Vomiting	frequency in last 24hrs *('0' if not vomiting)*															
Abdo pain	=none/ + =mild/ ++ =moderate/ +++ =severe															
Cough	(0, +, ++, +++)															
Fever(reported)	(0, +, ++, +++)															
EXAMINATION **CVS: Pallor**	(0, +, ++, +++)															
Resp(1):~Distress (SC/IC recess)	(0, +, ++, +++)															
Resp(2):~Chest signs	(N / Y)															
Mouth:	(N)ormal / (C)andida / (S)ores															
Pulse / Resp Rate *(if relevant)*						/	/	/	/	/	/	/	/		/	/
Other:																
Temperature (°C)	am / pm					/	/	/	/	/	/	/	/		/	/
LAB	MPS (0, +, ++, +++, ++++)															
	PCV															
	Other (e.g. Blood sugar -BS)															

D.3 Protocol for assessing inpatient symptoms and appetite

~ MOYO WEIGHT CHART & CCP ~

WEIGHT CHART

Please fill in:

1) Weight of the child:

NB RECHECK if weight changed.

~ Unexpectedly *(e.g. oedema better yet weight increased)*

OR

~ By large amount *(+/- 0.5kg in kwash patient; +/- 0.25kg in marasmus)*

2) Appetite for milk

E (excellent) = hungry, crying for more milk
G (good) – finishing *ALL* of milk *easily*
F (fair) = finishing *AT least* ¾ of milk OR finishing *all, but with difficulty*
P (poor) – finishing *less than* ¾ of milk ration
(NB if appetite POOR ➔ call for help *early* ➔ may need NG)

3) *(if on phase 1 or phase 2)*

= amount RUTF eaten, **to nearest ¼ bottle, *IN LAST 24hrs***

Critical Care Pathway Chart

Please Fill in:

1) Whether child on any fluids (ivi, resomal, other)
2) Whether child on O_2 or has NGT
3) CLINICAL HISTORY

CCP Question	***Ask (in Chichewa)***	***Record on file***
Progress *How is your child today?*	Kodi mwana wadzuka bwanji lero?	↓ if worse today ↔ if same as yesterday ↑ if better today
Stool:		
TODAY: *How many times has child opened bowels* ***since sunrise*** *today?*	Chitulukireni dzuwa lero, mwana wanu wachita chimbudzi kangati?	number of times today / e.g. x2 /
IN LAST 24HRS: *How many times has child opened bowels* ***from sunrise yesterday➔sunrise today***	Kuyambira dzulo momwe kunachera kufikira lero momwe kwachera, mwana wanu wachita chimbudzi kangati?	Number of times sunrise-sunrise (=24hrs) Record on *right* side of '/' e.g. .../ X3
What is stool like? *~ watery* *~ abnormally loose* *~ normal* *~ hard*	Chimbudzi cha mtundu wanji? ~ cha madzi madzi ~ cha phala-phala chachilendo ~ cholimba bwino bwino (~ cholimba kwambiri)	e.g. If watery: W If *abnormally* loose: L If normal N (C=constipated, unabnormally hard)
Vomiting *– how many times in 24hrs (sunrise-sunrise)*	Kuyambira dzulo momwe kunachera kufikira lero momwe kwachera, mwana wanu wasanza kangati?	number of times
Abdominal Pain *(in last 24hrs, sunrise-sunrise)*	Kuyambira dzulo momwe kunachera kufikira lero momwe kwachera, mwana wanu wakhala akumva kupweteka m'mimba?	SEVERITY: "Pang'ono" = mild, + ☹ "Mwapakatikati" = moderate ++ ☹ Kwambiri" = severe, +++ ☹
Cough *(in last 24hrs, sunrise-sunrise)*	Kuyambira dzulo momwe kunachera kufikira lero momwe kwachera, mwana wanu wakhala akukhosomola?	
Fever *(in last 24hrs, sunrise-sunrise)*	Kuyambira dzulo momwe kunachera kufikira lero momwe kwachera, mwana wanu wakhala akuthentha thupi?	

D.4 Inpatient 'phased feeding' protocol

Phase 1
(STABILIZATION phase)

WHAT:

F75 milk ~ amount according to weight

PHASE 1 PATIENTS ARE SEEN DAILY ON ROUNDS

WHO:

ALL patients

EXCEPT:

~ patients <6months old

→give F100 dilute

~ patients with VERY SEVERE oedema

→ see chart → reduce feed volume

WHEN:

ALL patients get phase 1 on admission.

It should continue for a MINIMUM of 1 day.

Phase 1
(STABILIZATION phase)

KEY MESSAGES FOR CARERS

WHAT IS WRONG WITH MY CHILD?

He/she is sick with severe malnutrition.

HOW CAN MY CHILD GET BETTER?

To get better, the child needs:
~ special medicine-foods (F75 milk; Chiponde)
~ medicines ~ as prescribed by the doctor / nurse

WHAT IS PHASE ONE FEEDING?

When a child first arrives on MOYO, the body is too sick and weak for normal food ~ it may get sicker unless feeding is done correctly.
Phase 1 feeding involves use of a special milk called 'F75'
'F75' is a special milk made just for sick malnourished children. It helps the body get stronger and prepares it for the next phase of feeding.

HOW MUCH F75 MILK DOES MY CHILD NEED?

It is important to give the right amount of F75 milk: not too much / not too little.
Always keep the 'ticket' saying how much milk your child needs:~
always show it to the kitchen staff who will then give you the correct amount

HOW OFTEN DOES MY CHILD NEED F75 MILK?

F75 needs to be given every 3 hours: 6am; 9am; noon; 3pm; 6pm; 9pm; midnight; 3am. (= 8 feeds per day)
Do not miss the night feeds ~ sick children can get worse if feeds are missed.

WHAT ABOUT BREAST FEEDING & OTHER FOODS?

CHILDREN STILL BREAST FEEDING SHOULD CONTINUE TO BREAST FEED
The best time to breast feed is immediately *before* getting f75 milk
No other foods should be given during phase one

WHAT SHOULD I DO IF MY CHILD IS HAVING PROBLEMS?

The child should be encouraged BUT NEVER FORCED to eat milk

If the child is finishing <3/4 of the milk, *GET HELP* → TELL NURSE / DRS

TRANSITION Phase

WHAT

The purpose is to slowly get used to RUTF whilst avoiding fluid overload. This is achieved by:

i) Continuing FULL F75 milk prescription (same as Phase 1)
AND
ii) Introducing RUTF ~ aim for target # pots/day according to chart

no other food / fluid is added for 1st 24-48hrs

iii) After 48hrs, all children should be offered extra water with RUTF

WARD ROUNDS

TRANSITION PHASE PATIENTS ARE SEEN DAILY ON ROUNDS

WHEN

A patient is ready to move onto transitional phase when:

a) ACTIVE Appetite has returned:

~ finishing whole phase1 milk amounts READILY & QUICKLY (it is *not* enough to be struggling to finish / if feeds are forced)

~ hungry or crying for more food

~ no longer needs NGT

AND

b) Clinically improving:

~ more alert & active

~ diarrhoea improving / no longer needing regular RESOMAL

AND

c) Oedema settling (if kwashiorkor):

~ visibly decreasing

~ weight reducing (certainly NOT increasing)

(N.B oedema *DOES NOT* have to have resolved completely)

TRANSITION Phase

MESSAGES TO GIVE TO CARERS

WHAT IS TRANSITION PHASE?

"Transition" phase feeds are given to children who are improving, so that they can *SLOWLY* get used to eating enough RUTF.

➔ Whilst on transition phase, 3 hourly milk feeds should continue exactly as before, *BUT:*

RUTF is added to the diet

WHAT IS RUTF (CHIPONDE)?

RUTF is a medicine-food which is:

energy-giving; body-building; health restoring

Eating enough RUTF is vital for the child to get better

HOW MUCH RUTF DOES MY CHILD NEED TO EAT TO GET BETTER?

The doctor/nurse will tell you how much your child should be aiming to eat per day. This depends on body size: *keep your ticket to help you remember.*

HOW SHOULD THE CHILD EAT RUTF

➔ RUTF should be eaten direct from the pot (using *CLEAN* hands or spoon)

➔ RUTF will make him/her thirsty & his/her the mouth dry, so:

~ The child should continue to drink milk, every 3 hours, as before.

➔ Eat spoonfuls of RUTF *before* and *between* mouthfuls of milk:

~ this will help wash down the RUTF, making it easier to eat.

~ do not wait until after milk to eat RUTF - else the stomach will become too full and the child be unable to eat the RUTF or will vomit.

➔ Sick children may not like to eat, so offer SMALL, REGULAR amounts::

~ start with a taste only / < ½ spoonful, together with each milk feed

~ *gradually* increase the amount of RUTF taken with each feed.

~ your ticket will show how many spoonfuls of RUTF you should be aiming for with each milk feed once appetite has returned fully

WHAT IF MY CHILD IS HAVING PROBLEMS EATING RUTF?

➔ Try mixing a small amount in with the milk to make it easier to swallow

➔ *NEVER* FORCE FEED! (This will only make a problem worse!!!)

If a child is vomiting or refusing RUTF take a break and continue milk feeds alone. Restart slowly. With time, the amount taken will gradually increase.

➔ Make sure the child has no mouth sores / candida: *ask the doctor for help!*

*** CHILDREN STILL BREAST FEEDING SHOULD CONTINUE TO BF ***

Phase 2
(REHABILITATION phase)

WHAT

Phase 2 feeds (on MOYO) include:

i) **RUTF (the MOST important food!)**
   ~ should *easily* finish at least 50% of target q amount

ii) **F75 milk**
   ~ same VOLUME as before
   ~ reduced FREQUENCY: only SIX times a days (i.e no longer needs midnight & 3am feeds)

iii) **Phala @ 6am, 6pm**

iv) **Extra water, as desired**

WARD ROUNDS

PHASE 2 PATIENTS ARE SEEN ONLY TWICE WEEKLY ON ROUNDS

(but clinical history / feed history is filled daily)

WHEN

A patient is not *moved* onto phase 2, but *moves* him/herself when:

a) Appetite is good enough:
   ~ is easily able to finish at least 50% of his/her daily RUTF target
   (N.B when reaches target, can have more if wanted)

b) Clinically stable
   ~ alert & active
   ~ admission problems improving / improved
   ➔ *DOES NOT NEED DAILY CLINICAN REVIEW*

AND

c) (If Kwashiorkor)
   ~ oedema *SETTLING* AND is not more than ++
   (NB does NOT have to have settled completely)

PHASE 2
(REHABILITATION phase)

MESSAGES TO GIVE TO CARERS

The child is continuing to get better and is making good progress:
He/she is now almost ready to leave hospital to finish treatment at home

WHY RUTF?

RUTF is the most important part of home treatment:
~ To continue to get better it is vital to continue to eat the full 'target' amount of RUTF that is given out
~ RUTF should not be shared (it is for malnourished children only)

WHAT ABOUT OTHER FOODS / WHAT IF THE CHILD IS STILL HUNGRY?

If still hungry after finishing the daily RUTF ration, it is OK to eat other foods
BUT
RUTF should be eaten as priority, *before* other foods
(children have small stomachs that will easily get filled ~ they will vomit if you try to give too much)

CHILDREN STILL BREAST FEEDING SHOULD CONTINUE TO BREAST FEED REGULARLY

HOW SHOULD THE CHILD EAT RUTF?

Basic instructions as for Transitional phase:
AND
Since the child is now eating more RUTF, he/she may be more thirsty than usual. He/she can now drink extra milk or water(boiled), according to thirst

OTHER

Use soap for child's hands and face before feeding. Keep food clean and lid on pot between feeds

With diarrhoea, never stop feeding. Give *EXTRA* food and *EXTRA* water.

FEED PROBLEMS
(moving back a phase)

WHAT

Sometimes, a child gets worse rather than better.
Children who deteriorate during their inpatient stay may need to move BACK to an earlier feeding phase.

WHEN

A child should move back to phase 1 if:

a) Appetite deteriorates
- **~ having significant problems eating RUTF**
- **~ refusing RUTF**

AND/OR

b) Clinically deteriorates

e.g.:
- **~ any complication needing IV infusion**
- **~ significant re-feeding diarrhoea**
- **~ tense abdominal distension**

AND/OR

c) Oedema worsens / develops fluid overload
- **~ increasing oedema in a child with kwashiorkor**
- **~ new onset oedema in a child with marasmus**
- **~ rapid increase in size of live**
- **~ other signs of fluid overload (bilateral crepitations; gallop rhythm; raised JVP)**

D.5 OTP protocols

(patients and their carers would be directed around various 'stations' of the OTP clinic, each focusing on a particular activity)

MOYO OTP:
~ station (1) ~
CLINIC BOOK & WEIGHT

REGISTER child's arrival in OTP *clinic* book

(check which group ~ 1 or 2 ~ write in CORRECT book)

↓

FILL OTP form:

HMIS #; child initials; today's date;
date originally discharged (to help find details if health passport lost);
which # visit this is(count in passport/ask mother)

↓

WEIGH child (*two* people to check)

If weight changed by more than (>) 1kg
→ CHECK WEIGHT AGAIN

↓

WRITE weight:

FIRST **on OTP form ~~~ *SECONDLY* in health passport**

↓

CHECK TARGET WEIGHT(80% wt/ht)
and
NUMBER OF VISITS & decide:

does this child need to go to station 2 OR direct to station 3?

MOYO OTP
~ station (2) ~
LENGTH & MUAC

NEED TO MEASURE LENGTH & MUAC IF…

i) CHILD nutritionally 'CURED'

= *REACHED target weight (80% wt/ht) on TWO consecutive visits*

OR

ii) 'FAILURE' of nutritional Therapy

= still not cured on 5th visit / 10 weeks

…if neither of above, go direct to station (3)

work in teams of two but:
*** MEASURE INDEPENDENTLY ***

BOTH REMEASURE if:

Difference of more than, >0.7cm btw lengths

Difference of more than, >0.5cm btw MUACs

↓

CALCULATE AVERAGE of measurements

↓

COMPARE to BASELINE length / MUAC:

BOTH REMEASURE if:

Length or MUAC~

decreased

OR

increased by > 2cm

↓

CALCULATE AVERAGE of LAST measures &
WRITE FINAL LENGTH/MUAC on OTP sheet

NB NOTE ON SHEET IF MEASURING HEIGHT (standing) rather than LENGTH (lying dow

MOYO OTP
~ station (3) ~
RUTF & SYMPTOM QUESTIONNAIRE

Complete patient questionnaire
(+ sign who is filling questionnaire)

↓

If has fever TODAY
➔ send to Malaria project for MPS / PCV before clinician review
(write request in health passport)

↓

IF ANY PATIENT SICK TODAY
=> ALERT CLINICIAN

MOYO OTP
~ station (4) ~
CLINICAN REVIEW
(+/- investigations, as appropriate)

REVIEW OTP FILE
(+ send back for review @ appropriate station if needed)

↓

REVIEW HISTORY
+/- EXAMINE PATIENT:

a) Clinically WELL but not cured
or
b)Clinically WELL AND CURED

↓

Discharge (D/C) to:
~ SFP (Supplementary Feeding Programme)
~ Other, as needed
(e.g. ARV/ Cotrim Clin/ Umodzi Pall. Care)

Clinically NOT well
or
NOT YET CURED

↓

Needs further R/V @ MOYO OTP:
Give date to come back in 2 weeks for:
~ more RUTF
~ further clinical review

MOYO OTP
~ station (5) ~
OTP REGISTER

REGISTER child in main OTP register

if D/C, write, in red pen:
a) SFP destination
b) final height (+change since baseline)
c) final MUAC (+ change since baseline)

↓

Give any appropriate medications

↓

Ensure carer understands any follow-up instructions

↓

If D/C: Give & explain SFP form

MOYO OTP
~ station (6) ~
RUTF distribution & clinic book

(check which group ~ 1 or 2 ~ write in correct book)

Give RUTF according to prescription
(N.B. children being discharged get sachets rather than bottles)

↓

Collect OTP clinic sheet & ensure all sections filled
(return to appropriate station if any missing details)

↓

Carer's left thumbprint in book
to confirm receipt of transport allowance & RUTF

↓

~ CARER & CHILD CAN GO HOM

Annex E. PRONUT study forms and questionnaires

E.1 Recruitment and consent

Page 1/1 **PRONUT form 01:** ***RECRUITMENT*** **HMIS no:** Y06__/__/__/__

1) RECRUITMENT

(all MOYO children are initially considered eligible for study)

1) EXCLUSION CRITERIA: ***(***** DO NOT RANDOMIZE / INCLUDE IN STUDY *****)***

1.1 Is child <6 months (==>needs F100 dilute feeds)

1 = yes, (<6months)	0 = no (>6m)
==> NOT eligible	***==> IS eligible***

2) CONSENT FOR TAKING PART IN STUDY:

2.1 If eligible, read consent form in Chichewa (or other appropriate lanuguage) ☐

(ensure understanding / refer any questions to senior investigator before signing) ***(tick when done)***

2.2 If eligible , does carer wish to take part in the study?

1 = yes:	0 = no
does want to take part	***does NOT want***

if NO ~ 2.2.1) If carer agrees, still complete all forms (to see if any differences btw study/non-study group?)

2.2.2) Thank carer & ask, if possible, to give reason for declining:

if YES~ *(give carer copy of study information / consent form)*

Name, signature (AND/OR) LEFT THUMBPRINT of carer _____

Name & signature of person obtaining consent _____

Explain that the study may not start immediately ~ only when the child is eligible for REHABILITATION feeds.
A second, verbal consent will then be requested to confirm willingness to take part
Any decision may be changed at any time without affecting the patient's clinical care

3) BASIC DETAILS

Ensure routine paperwork, incl weight & drug chart completely filled: **(tick when done)** ☐

If readmission: WRITE ADMISSIONS REGISTER IN RED: consider whether to use same or new HMIS number:

If *ORIGINAL* episode: **a)** ***AFTER*** **JULY 2006** (i.e. *SAME* HMIS YEAR) ***==> use OLD HMIS number***

b) ***BEFORE*** **JULY 2006** (i.e. *OLD* HMIS year) ***==> use NEW HMIS number***

******* WITHDRAWAL FROM STUDY / REVIEW OF ELIGIBILITY*******

4) ABSOLUTE WITHDRAWL *(==> NO MORE RUTF TO BE GIVEN)*

4.1 **Date of withdrawal:** ____ d/_____m/200__

4.2 **Timing of withdrawal:**

1 = pre-randomization	***2 = IP, post rnd.***	***3 = OTP, post rnd.***

4.3 **Give reason:**

1	NOT malnutrition *give correct Dx & details:*	1.1 RENAL (nephrotic / nephritic /other) 1.2 MALIGNANCY: 1.3 CARDIAC: 1.4 OTHER:
2	Patient carer request withdrawl *say why if possible*	
3	Other	

5) ELIGIBILITY FOR PRIMARY ANALYSIS *(==> CONTINUE RUTF but NOT for main analysis)*

5.1 **Eligible for primary analysis**

1 = yes	**0 = no**

5.2 **If no, why not?**

1) Cerebral palsy / syndrome	5) Other
2) Age >5years (60 months)	***DETAILS:***
3) Weight <4kg	
4) Not SAM (ie wt/ht>70%; >-3Z; MUAC>11.0cm)	

DATE: _____ / _____ / 2006 **Interviewer Initials:**

E.2 Baseline anthropometry

Page 1/1 **PRONUT form 02:** ***Anthropometry***

HMIS no: Y06__/__/__/__

Child Initials:

2) Anthropometry

1) CHILD:

1.1 Sex ..... | 1 = male | 2 = female |

1.2 Date of Birth ..... _____ d / _____m / _____y

1.3 Age today *(NB check DOB & AGE are consistent and correct)* _____yrs/_____months (***completed*** months)

1.4 Is date of birth: ..... | 1 = accurate | 2 = estimated | 99 = DK |

2) BASELINE ANTHROPOMETRY

2.1 BASELINE / ADMISSION WEIGHT:

	BASELINE WEIGHT			
checked by:			.	
rechecked by:				

2.1.1 Weight assessed by: | 1 = study team | 2= others |

2.1.2 If not study team, is it likely: | 1 = correct | 0 = wrong: if so, what is 1st correct wt:

2.2 BASELINE OEDEMA

Both repeat if any difference in grade:

	initials	*Oedema 1 ? ===>*	*Oedema 2 ? ===>*	BASELINE OEDEMA			
2.2.1				0	+	++	+++
2.2.2							

2.2.4 Oedema assessed by: | 1 = study team | 2= others |

2.2.5 If not study team, is it likely: | 1 = correct | 0 = wrong: if so, what is 1st correct oedema:

2.3 BASELINE LENGTH

2.3.1 **Which was done?** | 1 = length (measured lying down) | 2 = height (measured STANDING) |

***Both* repeat if: >0.7cm difference** (or, if readmission, height ↓ or ↑ >2cm)

	initials	*length 1 ? ===>*	*length 2 ? ===>*	*length 3*	***BASELINE LENGTH***
2.3.2					
2.3.3					cm

2.4 BASELINE MUAC

***Both* repeat if: >0.5cm difference** (or, if readmission, MUAC↓ or ↑>2cm)

	initials	*MUAC 1 ? ===>*	*MUAC 2 ? ===>*	*MUAC 3*	***BASELINE MUAC***
2.4.1					
2.4.2					cm

3) ARRIVAL AT MOYO / TFP

3.1 Check admission date(S) on front sheet is correct *tick when done* ☐

3.2 Admission: | 1 = direct from home to MOYO (via QECH U5/A&E) | 0 = referred / came via other

if not direct: 3.2.1 **admitted via WHERE:** *circle / code from list below*

3.2.2 **date orginally admitted/seen:** _____ d / _____m / _____y

1 = via PSCW
2 = readmission from MOYO OTP **(if readmission, check old notes)**
3 = referred from other FEEDING programme (SFP/OTP) - which:
4 = referred from other hospital / clinic (NOT feeding cente) - which:
5 = other (specify)

date ____d/ _____m/200___

E.3 Baseline clinical profile

Page 1/4 **PRONUT form 3:** ***Clinical*** **HMIS no:** Y06__/__/__/__

3) Clinical

HISTORY

1) HISTORY OF PRESENTING COMPLAINT (2 week history)

In the PREVIOUS ***2 WEEKS*** did (NAME) have: *(if not had, write '0' in 1st column and leave others blank)* ***99 = DK (all columns)***	**# days had problem** 0-14 days	**Was/Is problem:** 1= minor; 2= mod. 3= severe	**Where did you go for treatment?** *select one (or more) from list*	**Details of treatment:** *list* ***antibiotics*** *any other drugs* ***(NOT incl. those given today)***
1.1 Fever				
1.2 Diarrhoea (≥ 3 **abnormally loose or watery** stools/24h)				ORS? (1 = yes / 0 = no) ?other:
1.3 Vomiting				
1.4 Abdominal pain				
1.5 Fast / Difficult breathing (chest problem~*WITH* **OR** *WITHOUT* cough)				
1.6 Cough (but ***NO*** fast or difficult breathing)				
1.7 Oedema / swelling (say where started)				
1.8 Anorexia *(loss of appetite)*				
1.9 Flaky paint / kwashiorkor-type rash				
1.10 Other(1 - describe)				
1.11 Other(2-describe)				
1.12 Other(3-describe)				

TREATMENTS:

0 = Did not go for any treatment
1 = Continued treatment from MOYO OTP clinic (e.g cotrim, TB, other….)
2 = INPATIENT admission **where:**
3 = Outpatient/clinic (NOT incl. OTP today) **total # visits**
4 = from pharmacy
5 = from shop / marker / stall
6 = from relative/friend/elder
7 = from traditional healer
8 = other _____
99 = DK _____

2) BREAST FEEDING

2.1 Complementary feeding: **at what age were other foods 1st started?** _____months

2.2 ***Breast feeding:*** **Is (NAME) still BF?** | 1 = yes | 0 = no | 99 = DK |

if no:

3.2.1 **How old was he/she when BF stopped?** _____yrs/_____months

3.2.2 **Why was BF stopped** (ask re PMTCT advice):

3) PAST MEDICAL HISTORY *(ask to see health passport if available)*

3.1 Does carer have (NAME)'s health passport?

1 = yes (official passport)	2 = yes(temporary / exercise book)	0 = no

3.2 When (NAME) was born, what size was he/she?:

1 = normal (average) size or bigger	2 = smaller than average	3=very small	99 = DK

3.3 TB Has (NAME) had contact with anyone with TB?

1 = yes	0 = no	99 = DK

if yes:

3.3.1 **Is the contact:**	1=mother	2 = other female	2=father	3=other male	99 = DK
3.3.2 **Is the contact:**	1 = household	2 = other			99 = DK
3.3.3 **Is the contact sputum +ve**			1 = yes	0 = no	99 = DK
3.3.4 **Did child ever have:**	prophylaxis (=isoniazid only)		1 = yes	0 = no	99 = DK
	treatment(=multiple tabs)		1 = yes	0 = no	99 = DK

3.4 VCT & HIV Ever had an HIV test(*before* MOYO)?

1 = yes	0 = no	99 = DK

if yes: 3.4.1 **Result?**	0=NOT REACTIVE	1 = REACTIVE	2 = confidential	99 = DK
if (R): 3.4.2 **Is (NAME) taking REGULAR cotrim.**		1 = yes	0 = no	99 = DK
3.4.3 **Is (NAME) on a waiting list for ARVS?**		1 = yes	0 = no	99 = DK
3.4.4 **Is (NAME) already on ARVS?**		1 = yes	0 = no	99 = DK

if yes to 3.4.2 or 3.4.3: start date / planned start date _____d/ _____m/_____y

3.4.5 **Service provider**	1=QECH	2=DREAM	3 =other:

4) VACCINATIONS (see also health passport)

Has (NAME) ever had: *("definate" = documented / "probable" = carer thinks so)*

4.1 BCG	1 = yes, definite	2 = yes, probable	0 = no	99 = DK
4.2 DTP3	1 = yes, definite	2 = yes, probable	0 = no	99 = DK
4.3 Measles	1 = yes, definite	2 = yes, probable	0 = no	99 = DK

(N.B if not had measles -> arrange to give if >6 months age)

5) DEVELOPMENT & DISABILITY *(show pictures / check definitions)*

CAN (NAME) *USUALLY*:	*(A) ssessed*		*(R) eported*		
5.1 Walk alone (at least 5 steps)	0=NO **(A)**	1=YES **(A)**	2=NO **(R)**	3=YES **(R)**	99 = DK
5.2 Sit without support	0=NO **(A)**	1=YES **(A)**	2=NO **(R)**	3=YES **(R)**	99 = DK
5.3 Stand with assistance	0=NO **(A)**	1=YES **(A)**	2=NO **(R)**	3=YES **(R)**	99 = DK
5.4 Crawl on hands / knees	0=NO **(A)**	1=YES **(A)**	2=NO **(R)**	3=YES **(R)**	99 = DK
5.5 Walk with assistance	0=NO **(A)**	1=YES **(A)**	2=NO **(R)**	3=YES **(R)**	99 = DK
5.6 Stand alone for >10 seconds	0=NO **(A)**	1=YES **(A)**	2=NO **(R)**	3=YES **(R)**	99 = DK

5.7 Any concerns that (name) cannot do many of things normal for a child his/her age?

		1 = yes	0 = no	99 = DK
if yes: 5.7.1 **Circle any that apply:**	problems at birth	meningitis	cerebral malaria	
NOT had these problems	problems with hearing or vision		problems with hand movements	

5.7.2 **BRIEFLY describe:**

5.7.3 **What help or support are you getting?**

0 = None	2 = Physio	4 = other
1 = Cheshire homes (Feed the Children)	3 = MAP	99 = DK

6) OTHER STUDIES / RESEARCH PROJECTS

6.1 Is (NAME) taking part (currently or recently) in any other projects?

1 = yes	0 = no	99 = DK

Ask specificially about: ROTAVIRUS STUDY/ PMTCT/ ANY FEEDING STUDY

if yes: 6.1.1 DETAILS

6.1.2 STUDY ID / REF. No.

Date ____d/____m/200_ **Interviewer initials:**

HMIS no: Y06__/__/__/__

7) FAMILY HISTORY

(NOTE DETAILS OF HIV IF KNOWN)

7.1 **List *all* children born to same mother, including any who died**

	child	Approx date of Birth (day) / month / year	0=died/ 1=ill/ 2=well	details of illness or death *(incl month,year death if died)*
	oldest (#1)			
	2			
arrow	3			
to identify	4			
THIS	5			
child	6			
	7			
	8			
	9			

CLINICAL EXAMINATION

TIME: (after adm.) ***exact:*** 0 = <8hr | 1 = 8-24hr | 2 = 24-48h | 3 = >48hr

1) GENERAL

1.1 Admission temperature? ____._____ °C

1.2 Appearance / conscious level:

1 = normal & alert | 2 = lethargy / apathy | 3 =miserable/irritable | 4=low BCS

1.2.1 if BCS <5: /5

1.3 Dysmorphic features / Cerebral Palsy / Other severe disability — 1 = yes | 0=no; 99=DK

if yes ***describe:***

(comment on tone / reflexes / head circ ~ as needed)

1.4 Any traditional medicine charms or amulets? — 1 = yes | 0=no; 99=DK

2) HANDS, HAIR & SKIN

(see table for other relevant features)

2.1	**gen**	Hair changes (thin / fragile / discoloured)	0 = nil	1 = mild	2 = mod.	3 = severe
2.2	**gen**	Flaky-paint dermatosis	0 = nil	1 = mild	2 = mod.	3 = severe
2.3	**gen**	Clubbing?	0 = nil	1 = mild	2 = mod.	3 = severe
2.4	**(2)**	Fungal nail infection	1 = yes	0=no; 99=DK		
2.5	**(2)**	*Skin: (circle **which** present)* papular pruritic eruptions; herpes zoster; extensive warts; extensive molluscum	1 = yes	0=no; 99=DK		
2.6	**(4)**	Kaposi's sarcoma	1 = yes	0=no; 99=DK		

3) MOUTH

3.1	**gen**	Sores	0 = nil	1 = mild	2 = moderate	3 = severe
3.2	**(2)**	Angular chelitis; gingival erythema; recurrent ulcers	1 = yes	0=no; 99=DK		
3.3	**(3 / 4)**	Candida	0 = nil	1 = mild (tongue)	2 = mod. (also on mouth lining/palate)	3 = severe
3.4	**(3)**	Oral hairy leucoplakia; ulcerative teeth & gums (circle)	1 = yes	0=no; 99=DK		
3.5	**(4)**	Chronic herpes simplex *>1 month - on lips OR skin*	1 = yes	0=no; 99=DK		

4) MAJOR SYSTEMS

4.1	**(1)**	Persistent generalised lymphadenopathy *(>1cm @ ≥2 sites)*				1 = yes	0=no; 99=DK
4.2	**(2)**	Parotid enlargement *(persistent, unexplained)*				1 = yes	0=no; 99=DK
4.3	**(2)**	Recurrent, chronic URTI *current, with ≥1 event in last 6/12. e.g sinusitis, otitis media, bronchitis, croup, ear discharge*				1 = yes	0=no; 99=DK
4.4	**(2)**	Ear discharge (chronic, >1/12)				1 = yes	0=no; 99=DK
4.6	**gen**	Heart failure	1 = definate / probable		2 = possible		3 = unlikely
4.7	**gen**	Dehydration?		0 = nil	1 = mild	2 = mod.	3 = severe
4.8	**gen**	Peripheries		1 = warm(normal))		2 = cool	3 = cold
4.9	**gen**	Respiratory distress	0 = nil	1 = mild		2 = mod.	3 = severe
4.10	**gen**	Tachypnoea	1 = yes: note rate				0 = no
4.11	**gen**	Chest signs	1 = yes: describe				0 = no
4.12		*Is this severe pneumonia?*	1 = definate / probable		2 = possible		3 = unlikely
4.13	**(2)**	Hepatosplenomegaly	liver cm / Spleen cm			1 = yes	0=no; 99=DK
4.14		***OTHER (describe)***	1 = yes				0 = no
4.15		**PREVIOUS WEIGHT**	*copy growth chart from passport into file*			1 = done	0 = chart n/a

Previous highest weight: **WHEN (mth, year)** _____ / 0___ **WHAT:** _____ **kg**

Additional Hx *(see case definitions)*

(Circle and write "?" if approximate / 99(=DK) if unable to say)

5) OUTPATIENT VISITS: how many in last 6 months (***not*** incl this one) ***TOTAL #*** _____

Ask if any kwash/oedema/malnut NOT resulting in admission) 1 = yes | 0 = no | 99 = DK

Details: _____

6) INPATIENT ADMISSIONS: how many in last 6 months (*not* MOYO/*not* this one) ***TOTAL #*** _____

(Circle and write "?" if approximate / 99(=DK) if unable to say)

Details: _____

7) OTHER:

7.1	**(3)**	Any persistent diarrhoea (>14 days, unexplained, no response to Rx)				1 = yes	0=no; 99=DK
7.2	**(3)**	Any persistent fever? (>1 month, no response antibiotics/antimalarial				1 = yes	0=no; 99=DK
7.3	**(3)**	Any MODERATE malnut./SFP (NOT including after NRU discharge)?				1 = yes	0=no; 99=DK
7.4	**(3)**	Ever had pulmonary TB? (WHEN_____)				1 = yes	0=no; 99=DK
7.5	**(3)**	Ever had lymph node TB? (WHEN_____)				1 = yes	0=no; 99=DK
7.6	**(4)**	Ever had extrapulmonary / disseminated TB?				1 = yes	0=no; 99=DK
7.7	**(3)**	Unexplained blood problems? (anaemia/neutropenia/thrombocytope				1 = yes	0=no; 99=DK
7.8	**(3)**	Ever had severe recurrent pneumonia? ~ current AND ≥1 in last 6/12				1 = yes	0=no; 99=DK
		if yes was child admitted to hosptial?				1 = yes	0=no; 99=DK
		did child need oxygen whilst in hospital?				1 = yes	0=no; 99=DK
7.9	**(4)**	Ever had PCP pneumonia?				1 = yes	0=no; 99=DK
7.10	**(3)**	Ever been diagnosed with HIV chronic lung disease or LIP?				1 = yes	0=no; 99=DK
7.11	**(4)**	Recurrent severe bacterial infection?				1 = yes	0=no; 99=DK
		(e.g. empyema; pyomyositis; bone or joint infection; meningitis ~ NOT PNEUMONIA)					
7.12	**(4)**	CNS problems: HIV encephalopathy; crypro meningitis; lymphoma; PML				1 = yes	0=no; 99=DK
7.13	**(4)**	Other: CMV retinitis; HIV rectal fistula; cryptosporidiosis; isosporiasis; herpes				1 = yes	0=no; 99=DK
7.14	**(4)**	Ever had severe malnutrtion / admitted to NRU (OR CTC programme				1 = yes	0=no; 99=DK
		if yes how many admissions before this?	#	when LAST admitted			
		where admitted	1=MOYO	2 = other			99 = DK
		did child reach cure?	0 = no	1 =yes: WHEN discharged?			99 = DK
		did child have SFP after?	0 = no	1 =yes: WHERE			99 = DK

Date ____d/____m/200_ = **CLINICIAN initials**

E.4 Baseline geographical details and verbal map

Page 1/3 **PRONUT form 4:** ***Geography*** **HMIS no:** Y06__/__/__/__

4) Geography

1 MAIN RESIDENCE (= home of main carer / where child spends *MOST* time)

1.1 DISTRICT _____

1.2 TA / WARD _____

1.3 VILLAGE / TOWNSHIP _____

1.4 IS RESIDENCE:	1 = urban	2 = rural	99=DK

2) MAP LOCATION ***(MAIN RESIDENCE)***

To help locate residence on map, please state:

2.1 NEAREST ***(GOVERNMENT)*** SCHOOL(S)

Name (must include school on the map):

Distance of school from residence:

2.2 NEAREST ***(GOVERNMENT)*** HEALTH CENTRE(S)

Name (must include health centre on the map):

Distance of health centre from residence:

2.3 BEST GUESS LOCATION

MAJOR grid square	LETTER	NUMBER
small grid square	letter	number

3) ACCESS TO MOYO FROM HOME

Decribe your journey from home to MOYO:

	From	To	Travel means*	**Time (if known)	Cost (MK)
3.1	**Home**		walk		
3.2					
3.3					
3.4					
3.5					
3.6					

codes: ***TRAVEL:** 1=walk / 2=bicycle / 3=minibus / 4=ambulance / 5=hitchhike / 6=other

****TIME** *If possible, estimate # **(99 = DK)***

if unable to say in hours: +=short time; ++=medium time; +++=long time (as percieved by carer)

4) DIRECTIONS TO RESIDENCE

(start from major local landmark - e.g school, health centre, shop)

Please include names of at least two people to ask to help find house:

+ WHO are they?

1)

2)

3)

5) SECONDARY RESIDENCE *(i.e. 'home' village / other place where spends SIGNIFICANT time)*

5.1 DISTRICT

5.2 TA/WARD

5.3 VILLAGE / TOWNSHIP

5.4 REASON FOR SECONDARY RESIDENCE

1=work	2 = family / 'home' district	3 = farmland	4 = other	99 = DK

6) Directions to residence ***(SECONDARY RESIDENCE ~ if applicable)***

Use local clinic / school (ON MAP) as landmark

6.3 *Please include names of at least two people to ask to help find house:*

+ WHO are they? 1)

2)

6.4 ***BEST GUESS LOCATION***

MAJOR grid square		LETTER	NUMBER	
small grid square		letter	number	

Date ____d/____m/200_ **Interviewer initials:**

HMIS no: Y06__/__/__/__

CHILD INITIALS:

7) DIRECT DROP / GPS *(Main residence)*

7.1 DATE ____d/____m/_____y

7.2 GIVEN LIFT FROM	***1 = inpatient discharge***	***2= OTP clinic***	***3 = other***

7.3 Description of home location:

a) Basic directions from QECH:

b) Where to leave car:

c) Approx time walking from car: mins

d) Landmarks / directions to help find house

7.4 GPS TECHNICAL Number of satellites: #

Accuracy meters

7.5 WAYPOINT NUMBER #

7.6 GPS COORDINATES

7.6.1	Elevation	meters
7.6.2	South	° ' . "
7.6.3	East	° ' . "

Date ____d/____m/200_ **Driver initials:**

E.5 Socioeconomic profile

Page 1/2 **PRONUT form 05:** ***SES*** **HMIS no:** Y06__/__/__/__

5) Socio-economic status

1) CARERS

1.1 CARER **Who is with child now / answering this questionairre?**

1 = mother	4 = aunt	6 = other family~ who	
2 = father	5 = uncle	7 = other non-family~who	
3 = grandmother	6 = neighbour		99 =DK

1.2 MAIN (usual) CARER | 1=same as in qn above | 2 = other, from list above:

If main carer is not with child why not:

1.3 PARENTS

1.3.1 Is mother alive?	1 = yes	0 = no	99 = DK

if mother alive but is not main carer, why not?

1.3.2 Is father alive?	1 = yes	0 = no	99 = DK
1.3.3 If both alive, are they together?	1 = yes	0 = no	99 = DK

1.4 Mother's D.O.B (if known) _____d / _____m / 19____ | 99 = DK

1.5 ***If DOB not known, how old was mother when (NAME) was born*** years (99 = DK)

1.6 WHAT IS / WAS *MAIN* OCCUPATION OF: *(describe AND write correct code in box)*

1.6.1 Mother	describe:	code
1.6.2 Father	describe:	code
1.6.3 (Main carer - if not parent)		code

Active	Unemployed	Inactive
1 = mlimi / ganyu	6 = worked before, seeking work	9 = never worked, not looking
2 = employee	7 = worked before , not looking for work	10 = housewife
3 = family business		11 = student
4 = self-employed	8 = never worked before, looking for work	12 = other
5 = employer		99 = DK

1.7 LITERACY *= Can read/write ~ (use 'test' sentence to check)*

1.7.1 Mother	1 = yes	0 = no	99 = DK
1.7.2 Father	1 = yes	0 = no	99 = DK
1.7.3 (MAIN Carer - if not parent)	1 = yes	0 = no	99 = DK

1.8 HIGHEST EDUCATION LEVEL ACHIEVED *(write correct code in box)*

1.8.1 Mother	
1.8.2 Father	
1.8.3 (MAIN Carer - if not parent)	

None *= 0*

Primary *S1 = 1 S2 = 2 S3 = 3 S4 = 4 S5 = 5 S6 = 6 S7 = 7 S8 = 8*

Secondary *F1 = 9 F2 = 10 F3 = 11 F4 = 12 F5 = 13 F6 = 14*

Higher *University / other higher = 15 other =16_____ 99 = DK*

2 FAMILY SOCIOECONOMIC STATUS **~ WEALTH INDEX DHS**

*THIS REFERS TO THE HOME OF THE **MAIN** CARER / WHERE THE CHILD **USUALLY** STAYS*

2.1 GENERAL

Tenure	1 = owner	2 = rented	3 = other	99 = DK

How many sleeping rooms are there? (excl. bathroom/storerooms/garage) .....

How many household members are there? ..... #

(people who usually stay in the same house together; eat meals together; make provisions for food together)

2.2 HOUSEHOLD POSESSIONS & ASSETS

	In the dwelling is there:		
Electricity	1 = yes	0 = no	99 = DK
A radio	1 = yes	0 = no	99 = DK
A bicycle	1 = yes	0 = no	99 = DK
A motorcycle (or motorscooter)	1 = yes	0 = no	99 = DK
A car (or truck)	1 = yes	0 = no	99 = DK
A paraffin lamp	1 = yes	0 = no	99 = DK
An oxcart	1 = yes	0 = no	99 = DK
A mosquito net	1 = yes	0 = no	99 = DK
A television	1 = yes	0 = no	99 = DK
A cellphone	1 = yes	0 = no	99 = DK
A telephone (landline)	1 = yes	0 = no	99 = DK
A bed with a mattress	1 = yes	0 = no	99 = DK
A sofa set	1 = yes	0 = no	99 = DK
A table and chair(s)	1 = yes	0 = no	99 = DK
A refrigerator	1 = yes	0 = no	99 = DK
A domestic worker not related to household head	1 = yes	0 = no	99 = DK
Do members of household work their own agricultural land?	1 = yes	0 = no	99 = DK

2.3 WATER SOURCES

What is the MAIN source of drinking water for the household?

1 = piped INSIDE DU (dwelling unit)	5 = open well (SHARED/PUBLIC)	9 = surface water
2 = piped OUTSIDE DU (in yard/plot);	6 = borehole/protected well (OWN plot)	(river, stream, pond, lake, dam)
3 = piped (COMMUNITY stand pipe)	7 = borehole/protected well (SHARED/PUBLIC)	10 = other
4 = open well (OWN yard / plot)	8 = from a spring	99 = DK

2.4 TOILET

What is the MAIN type of toilet used by household members?

1 = own (exclusive) flush	4 = traditional pit latrine (SHARED)	7 = no facility (bush / field)
2 = shared flush toilet	5 = VIP (ventilated improved pit) latrine (OWN)	10 = other
3 = traditional pit latrine (OWN)	6 = VIP latrine (SHARED)	99 = DK

2.5 FLOORING

What is the MAIN type of flooring in your dwelling?

1 = nicely finished *(circle which)*	2 = finished (cement, vinyl/asphalt strips)	10 = other
(parquet/polished wood; ceramic tiles; carpet)	3 = wood or plank	
	4 = natural materials (earth / sand / dung)	99 = DK

2.6 ROOFING

What is the MAIN type of roofing in your dwelling?

1 = cement	4 = iron sheets	10 = other
2 = asbestos	5 = natural materials	
3 = iron and tiles		99 = DK

2.7 FUEL FOR COOKING

What fuel does the household MAINLY use for cooking?

1 = electricity	4 = charcoal, coal or lignite	10 = other
2 = gas (LPG / natural gas / biogas)	5 = wood or straw	
3 = paraffin / kerosene	6 = dung	99 = DK

2.8 DOMESTIC ANIMALS

How many of the following are owned: *(0 if nil, 99 if DK)*	goats	pigs	cattle	sheep	chickens

Date **____d/____m/200__** **Interviewer Initials:**

E.6 OTP review

Page 1/2 **PRONUT form 07:** ***OTP Review***

HMIS no: Y06__/__/__/__

Child Initials:

7) OTP Review

date _____d/_____m/_____y

1) VISITS

1.1 **Date originally discharged from MOYO?** _____d/_____m/_____y

1.2 **Which number OTP is this? (e.g 1st, 2nd, 3rd etc)** visit #

PLEASE CHECK:
1) MUAC @ EVERY VISIT (same rules as below); 2)CD4 at 1st/2 week visit(=routine test)

2) ANTHROPOMETRY

2.1 **TODAY's WEIGHT:**

checked by:			.	
rechecked by:				

2.2 **?CURE:** **(= target weight (>80% wt/ht) on TWO consecutive visits)** 1 = yes | 0 = no

2.3 **?NUTRITIONAL FAILURE** **(= not cured @ 5th visit/10 weeks OTP)** 1 = yes | 0 = no

if no, GOTO q.3

if any YES:

2.4 ***DISCHARGE LENGTH*** *Both* repeat if: >0.7cm difference; OR if child shorter OR if grown >2cm

	initials	*length 1*	*length 2*	*length 3*	***FINAL LENGTH***
2.4.1					
2.4.2					cm

2.4.3 CIRCLE **HEIGHT** if height rather than length measured

2.4.5 **Length increase from baseline** cm

2.4.6 ***Is baseline length likely*** 1 = correct | 0 = incorrect

2.5 ***DISCHARGE MUAC*** *Both* repeat if: >0.5cm difference; OR if MUAC shrunk OR if increased >2cm

	initials	*MUAC 1*	*MUAC 2*	*MUAC 3*	***FINAL MUAC***
2.5.1					
2.5.2					cm

2.5.4 **MUAC increase from baseline** cm

2.5.5 ***Is baseline MUAC likely*** 1 = correct | 0 = incorrect

3) FOOD & APPETITE

3.1 ***RUTF (Ready-to-Use Therapeutic Foods)***

How many bottles were:

3.1.1 **Given @ last visit** *# pots given*

3.1.2 **Average number pots eaten / day** *# pots eaten/day*

3.1.3 **Left UNFINISHED** *# pots unfinished*

if any unfinished, why:

3.1.4 **IF ALL POTS eaten *by child*, how many days ago were they finished** ***# days***

3.1.5 **Any problems eating the RUTF?** 1 = yes | 0 = no | 99 = DK

If YES ***Describe:***

What was done?:

Did it help?

3.2 ***OTHER FOODS ~ feed programmes / projects***

Is (NAME) getting food from other projects / feed programme? 1 = yes | 0 = no | 99 = DK

If YES 3.2.1 *Details*: **what / from who / how much / how often?**

4) CLINICAL PROGRESS (2 week history)

In the PREVIOUS ***2 WEEKS***, did (NAME) have: *(if not had, write '0' in 1st column and leave others blank)* ***99 = DK (all columns)***	**# days had problem** 0-14 days	**Was/Is problem:** 1= minor; 2= mod. 3= severe	**Where did you go for treatment?** *select one (or more) from list below*	**Today, is problem:** 0 = all gone 1 = better; 2 = same; 3 = worse	**Details of treatment:** *list* ***antibiotics*** */ ORS / any other drugs* ***(NOT incl. those given today)***
4.1 Fever					
4.2 Diarrhoea (≥ 3 **abnormally loose or watery** stools/24h)					ORS? (1 = yes / 0 = no) ?other:
4.3 Vomiting					
4.4 Abdominal pain					
4.5 Fast / Difficult breathing (chest problem~*WITH* **OR** *WITHOUT* cough)					
4.6 Cough (but ***NO*** fast or difficult breathing)					
4.7 Other(1)					
4.8 Other (2)					

TREATMENTS:

0 = Did not go for any treatment
1 = Continued MOYO treatment given @ last visit (e.g cotrim, TB, other….)
2 = INPATIENT admission
3 = Outpatient/clinic (NOT incl. OTP today) **total # visits**
4 = from pharmacy
5 = from shop / marker / stall
6 = from relative / friend / elder
7 = from traditional healer
8 = other
99 = DK

interviewer initials

5) ANY INPATIENT ADMISSIONS NOT ALREADY MENTIONED? 1 = yes | 0 = no | 99 = DK

if yes: **dates:** *from* *to*
diagnosis / details:

6) ANY OTHER MEDICINES NOT ALREADY MENTIONED? 1 = yes | 0 = no | 99 = DK

ASK RE COTRIM / TB /HIV	*WHAT:*	*x per day*	*# days*

CLINICIAN TO COMPLETE REST OF FORM

6) CLINICAL EXAMINATION

6.1 **Detailed examination:~**
(only if problems / unwell)

6.2 **DIAGNOSIS:** 1 = well 2 = URTI 3 = LRTI 4 = GE 5=other _____

7) INVESTIGATIONS NEEDED? 0 = no | 1 = yes (needs today) | 2 = yes(review of Ix ordered @ last visit)

7.1 **MPS** (0 = neg; 1 = +; 2 = ++; 3 = +++)
7.2 **PCV** PCV %
7.3 **OTHER(e.g CXR, mantoux)**
7.4 **CD 4 (routine test for HIV ® children)** 0 = to do today (tick when done) **RESULT(%)**

8) OUTCOME

1= POOR ==> severe problem ideally needing readmission
if readmission needed, does carer agree: 1 = yes | 0 = no *details:*
2= FAIR ==> problem(s), but OK for home treatment
3= GOOD/not YET cure ==>needs further review
4= GOOD/CURE ==> FOR D/C *(=achieved 80% target wt on TWO consecutive visits)*
5= FAILURE OF NUTRITIONAL THERAPY *(= not cured @ 5th visit/10 weeks OTP)*
6= Other (e.g transfer out) _____

9) TTO MEDICATIONS(s)
(circle all that apply ~ incl TB/ARV etc
Note any ***relevant*** *details*
e.g dose; duration; start date

0 = nil		4 = Iron
1 = cotrimoxazole		5 = other (1)
2 = ARVs	started on:	6 = other (2)
3 = TB meds	started on:	7 = other (3)

10) FOLLOW-UP:

10.1 Clinical (circle ALL that apply)

0 = NONE ~ no routine fup needed	4 = ARV clinic - start date:~
1 = CONTINUE MOYO fup in 2/52	5 = TB clinic
2 = ARV staging clinic	6 = Disability clinic: which_____
3 = Cotrim clinic	7 = Other

10.2 SFP 1 = yes: ~ *which:~* | 0 = no

Date ____**d/**____**m/200_** **Clinician initials**

Annex F. PRONUT study additional details and results

F.1 RUTF quality control: concentration of Synbiotic organisms

Table 43 Quality control testing of randomly selected RUTF batches

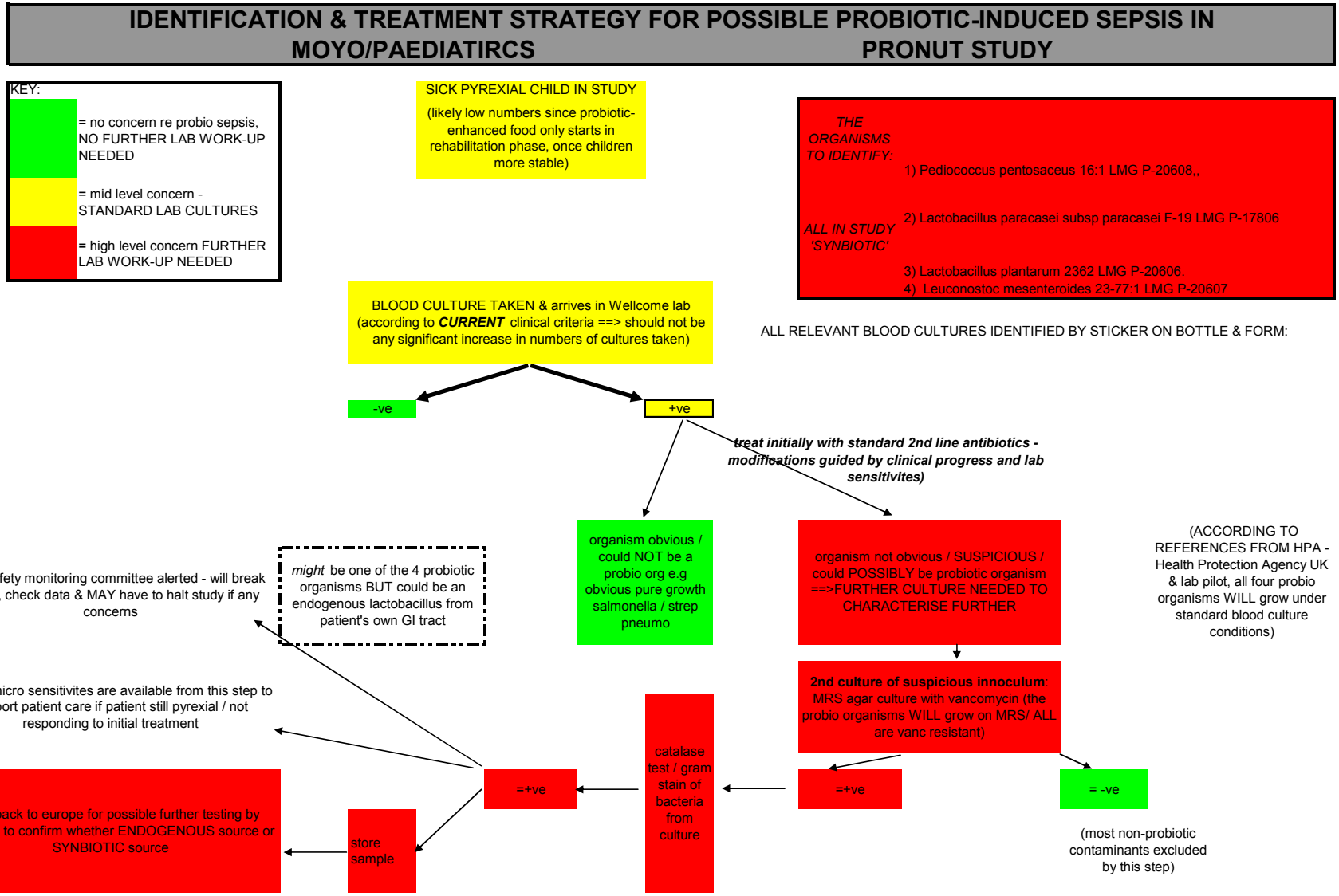
	(a) **SYNBIOTIC GROUP** concentration of lactic acid bacteria *(date of lab testing)*	**(b)** **daily dose of probiotic** (av. 1.19 pots RUTF /day eaten: 300g RUTF per day = 5.95g Synbiotic/ day)	**(c)** **CONTROL GROUP** concentration of lactic acid bacteria *(date of lab testing)*	**(d)** daily **dose LAB** average 1.19 pots RUTF /day eaten: 300g RUTF per day
RUTF date of manufacture	CFU/g	= (a) * 300	CFU/g	= (c) * 300
15th Jan 2006 *(Pilot batch not used in study. Laboratory incubated @ 30°C)*				
Baseline (2 weeks after manufacture)	6.43 x 10^9 *(31st January 2006)*	**1.93 x 10^12**	n/a	**n/a**
After 1 month	5.03 x 10^8 *(28th February 2006)*	**1.51 x 10^11**	n/a	**n/a**
After 2 months	2.23 x 10^8 *(31st March 2006)*	**6.69 x 10^10**	n/a	**n/a**
After 3 months	3.50 x 10^8 *(28th April 2006)*	**1.05 x 10^11**	n/a	**n/a**
13th Jul 06 *(this and all subsequent batches as used in study)*				
Baseline (2 weeks after manufacture)	1.9 x 10^8 *(August 2006)*	**5.70 x 10^10**	3.3 x 10^2 *(August 2006)*	**9.9 x 10^4**
Late (2 months after manufacture)	3.65 x 10^8 *(September 2006)*	**1.10 x 10^11**	<1*10^2 *(September 2006)*	**<3.0 x 10^4**
10th Aug 06				
Baseline sample	3.16 x 10^8 *(September 2006)*	**9.48 x 10^10**	5.5 x 10^2 *(September 2006)*	**1.7 x 10^5**
Late sample	n/a	**n/a**	2.8 x 10^5 *(October 2006)*	**8.4 x 10^7**
Longer term stability (approx 5 months after manufacture)	2.7 x 10^8 *(January 2007)*	**8.10 x 10^10**	n/a	**n/a**
16th Sept 06				
Baseline sample	2.2 x 10^8 *(October 2006)*	**6.60 x 10^10**	2.8 x 10^6 *(October 2006)*	**8.4 x 10^8**
Late sample	1.6 x 10^8	**4.80 x 10^10**	n/a	**n/a**
10th Oct 06				
Baseline sample	2.3 x 10^8 *(November 2006)*	**6.90 x 10^10**	3.0 x 10^3 & <1 X 10^3 *(November 2006)* (analysed x2)	**9.0 x 10^5**
Late sample	n/a	n/a	n/a	n/a
Longer term stability	5.6 x 10^7 *(January 2007)*	**1.68 x 10^10**	n/a	**n/a**
5th Nov 06				
Baseline sample	n/a	**n/a**	n/a	**n/a**
Late sample	1.2 x 10^8 *(January 2007)*	**3.60 x 10^10**	<1 x 10^5 *(January 2007)*	**<3.0 x 10^7**
3rd Jan 07				
Baseline sample	1 x 10^8 *(January 2007)*	**3.00 x 10^10**	<1 x 10^5 *(January 2007)*	**<3.0 x 10^7**
Late sample	n/a	**n/a**	n/a	**n/a**

n/a = not available (sample not sent since did random selection of some batches, but not routine testing of all).

Notes: a) Concentrations apparently going UP with time are due to non-homogenous mixing.

b) Some control batches had small concentrations of lactic acid bacilli (LAB) due to non-sterile nature of milk powder used in the RUTF recipe. The lab assay could not distinguish between Synbtioic2000 Forte™ LAB and others.

F.2 Possible probiotic sepsis laboratory protocol



F.3 Baseline clinical characteristics (detailed)

Table 44 Baseline clinical characteristics in detail

		Synbiotic (n=399)	Control (n=396)
Symptoms in 2 weeks prior to admission (total patient days with symptom standardized per 1000 days observation)			
	(Total patient days of observation)	*(5586)*	*(5544)*
	Diarrhoea	310	268
	Vomiting	180	141
	Abdominal Pain	190	151
	Fast and/or difficult breathing	44	42
	Cough	288	269
	Fever	245	221
	Oedema	296	271
	Anorexia	335	293
	Flaky paint dermatosis	84	90
	Other	156	124
Outpatient consultations in 2 weeks prior to admission			
	One or more outpatient visits	276/388 (71.1%)	273/383 (71.3%)
Medication use in last 2 weeks			
	Any medication	347/388 (84.9%)	335/381 (87.9%)
	If used medications were antibiotics used? (if able to	156/306 (51.0%)	148/299 (49.5%)
Past medical history / admissions (% of patients)			
	Any inpatient admissions (last 12 months, not SAM)	75/382 (19.6%)	72/372 (19.4)
	Any outpatient visits in last 6 months	336/374 (89.8%)	340/370 (91.9%)
	Any previous admissions for SAM (EVER)	55/390 (14.1%)	49/382 (12.8%)
	Any outpatient based supplementary feeding (last	90/387 (23.3%)	81/376 (21.5%)
Feeding history			
	Currently breast feeding	104/393 (26.5%)	114/388 (29.4%)
	If not breast fed, age at which stopped (mean	19.6 ± 8.3	19.6 ± 8.3
Growth chart in health passport (if available)			
	Weight decreasing on chart	152/232 (65.5%)	142/237 (59.9%)
Reported Birth-weight			
	"Normal or bigger than normal"	340/377 (90.2%)	339/376 (90.2%)
Immunization status (% of children recorded or reported immunized)			
	BCG	384/389 (98.7%)	375/378 (99.2%)
	DTP (all 3 doses)	376/390 (96.4%)	370/378 (97.9%)
	Measles	323/380 (85.0%)	330/372 (88.7%)
Admission investigations			
	PCV (mean ± sd)	31.5 ± 6.7	31.1 ± 7.1
	Malaria parasites on peripheral blood smear (any)	25/377 (6.6%)	28/357 (7.8%)
TB			
	Had pulmonary TB in the past (ever)	15/391 (3.8%)	8/379 (2.1%)
	Diagnosed with TB at any time during programme	19/396 (4.8%)	11/390 (2.8%)
Inpatient antibiotics at any time whilst on ward (all patients had 1st line antibiotic,			
	Had 2nd line antibiotics (chloramphenicol /	192/396 (48.5%)	181/390 (46.4%)
	Had 3rd line antibiotics (ceftriaxone)	31/396 (7.8%)	31/390 (7.9%)
Inpatient days PRIOR to randomization			
	Total inpatient days observation prior to	***1458***	***1424***
	Median inpatient days prior to randomization +/- IQR	2 +/-1	2 +/-1
Inpatient Symptoms PRIOR to randomization, total patient days with symptom per 1000 days observation			
	days where no observation noted on chart	*54*	*52*
	Abnormally loose/watery stool (any)	462	473
	Diarrhoea (≥3 loose/watery stool / 24hrs)	300	272
	Severe diarrhoea (≥6 loose/watery stool / 24hrs)	73	65
	Vomiting (any)	295	258
	Abdominal pain (any)	273	268
	Cough (any)	552	540
	Fever (any, reported)	442	471
	Fever (documented, >37.5)	291	270
Other signs & symptoms (symptoms either reported by carer or documented in child 'health			
	Hair Changes (any)	312/392 (79.6%)	327/385 (84.9%)
	Dermatosis (any)	118/380 (31.1%)	115/381 (30.2%)
	Finger clubbing (any)	35/396 (8.8%)	25/389 (6.4%)
	Oral sores (any severity)	73/394 (18.5%)	61/387 (15.8%)
	Angular chelitis	91/392 (23.2%)	69/382 (18.1%)
	Oral candida (any)	127/391 (32.5%)	105/387 (27.1%)
	Generalized lymphadenopathy	36/396 (9.1%)	40/388 (10.3%)
	Parotid enlargement	7/394 (1.8%)	6/384 (1.6%)
	Reported recurrent Upper Respiratory Tract	34/393 (8.7%)	41/381 (10.8%)
	Reported chronic ear Discharge	25/392 (6.4%)	33/381 (8.7%)
	Hepatospenomegaly	39/396 (9.8%)	26/390 (6.7%)
	Reported persistent diarrhoea	97/388 (25.0%)	74/375 (19.7%)
	Reported persistent fever	33/387 (8.5%)	32/375 (8.5%)
	Unexplained blood problems	22/391 (5.6%)	13/380 (3.4%)
	Reported Severe Recurrent Pneumonia	26/390 (6.7%)	27/380 (7.1%)
	Reported Recurrent severe bacterial infection	7/389 (1.8%)	3/380 (0.8%)
CD4 count (%) ~ taken at 1st outpatient visit, 2 weeks after discharge from ward, seropositive children only			
	CD4 <20% (of seropositive children in whom CD4	61/92 (66.3%)	67/103 (65.0%)
	CD4% (mean)	18.3 ± 9.6 (n=92)	17.8 ± 10.1 (n=103)

F.4 Baseline family and socioeconomic status (detailed)

Table 45 Baseline family and socioeconomic status in detail

	Synbiotic (n=399)	Control (n=396)
Family Status		
Mother		
Mother alive	358/387 (92.5%)	350/384 (91.1%)
Main carer is mother	329/387 (85.0%)	321/384 (83.6%)
Mother's occupation is housewife	217/379 (57.3%)	196/377 (52.0%)
Mother literate	246/378 (65.1%)	243/366 (66.4%)
Mother educated to secondary school level or above	64/371 (17.3%)	81/368 (22.0%)
Father		
Father alive	357/383 (93.2%)	353/382 (92.1%)
Parents together (if both alive)	261/329 (79.3%)	239/321 (74.5%)
Father is in paid employment	278/372 (74.7%)	277/359 (77.2%)
Father literate	334/364 (91.8%)	315/343 (91.8%)
Father educated to secondary school level or above	139/284 (48.9%)	140/269 (52.0%)
Socioeconomic status		
Family own their own house	234/386 (60.6%)	234/382 (61.3%)
Household assets		
Electricity	39/386 (10.1%)	49/382 (12.8%)
Radio	220/385 (57.1%)	220/382 (57.6%)
Bicycle	73/386 (18.9%)	66/382 (17.3%)
Parafin Lamp	295/385 (76.6%)	307/382 (80.4%)
Mosquito net	223/386 (57.8%)	225/380 (59.2%)
TV set	33/386 (8.5%)	30/382 (7.9%)
Cellphone	57/386 (14.8%)	43/382 (11.3%)
Bed with mattress	152/386 (39.4%)	127/380 (33.4%)
Fridge	8/385 (2.1%)	8/382 (2.1%)
Family own their own land	231/382 (60.5%)	223/381 (58.5%)
Main household water source		
Piped	208/386 (53.9%)	217/382 (56.8%)
Borehole / protected well	132/386 (34.2%)	117/382 (30.6%)
Main household toilet		
Traditional pit latrine	373/386 (96.6%)	367/382 (96.1%)
Main household fuel for cooking		
Charcoal	176/385 (45.7%)	166/380 (48.5%)
Wood or straw	202/385 (52.5%)	204/380 (53.7%)

Annex G. FUSAM study forms and questionnaires

G.1 Main study form

Page 1/6

HMIS no: Y06___/___/___/___

INITIALS

MOYO 1 year follow-up

1) DATES

1.1 Date of this follow-up VISIT _____d / _____m /2007

2) OUTCOME OF FOLLOW-UP VISIT

2.1 What was outcome of follow-up visit?

1 =	***Child seen ~***
	1a = seen @ OTP | 1b = seen @ field visit | 1c=other
2 =	***Child not seen: but information reliable*** *(e.g from main carer / close relative)*
3 =	***Child not seen: information may be unreliable*** *(e.g family friend or neighbour)*
4 =	***Unsuccessful search*** *(child not found, no information available)*

3) CARER / PERSON ANSWERING QUESTIONS

3.1 Who is child's main carer / answering this questions now?

1 = mother	4 = aunt	6 = other family~ who	99 =DK
2 = father	5 = uncle	7 = other non-family~who	
3 = grandmother	6 = neighbour		

3.2 Who was ORIGINALLY with child whilst on MOYO | 1=same as above | 2=other, from list: |

If different, why has carer changed? | 1 = death | 2=sickness | 3=other | 77 = n/a | 99=DK |

EXPLAIN REASON FOR FOLLOW-UP VISIT + obtain verbal consent to ask further questions

3.3 Does carer agree to answer questions about progress since MOYO? | 1 = yes | 2 = no | 77=n/a |

4) HOW IS CHILD NOW?

4.1 How is child now (or how was child when last seen?)

1 =	***Child DIED (fill table opposite: ask re problems prior to death)***
if died: *WHERE DIED*	*1 = home* | 2 = hospital | 3=other | 99 = DK
if hospital, which:	2a= hospital MOYO | 2b=QECH/PSCW | 2c=hospital other:
2 =	***Child well (according to reporter)***
3 =	***Child still sick (according to reporter)***
99 =	***Don't know / no info available***

4.2 **Date of final outcome** (i.e. date today if alive OR date died OR date last seen if has since moved away)

(if approximate, put circle around box) _____d / _____m /_____y

5) FOLLOW-UP WEIGHING / GROWTH MONITORING

5.1 **Is the child's health passport available to see now?** | 0 = no | 1 =yes | 77 = NA |

5.2 **Has the child been weighed since MOYO** (not SFP) | 0 = never | 1 =yes | 77 = NA | 99 = DK |

5.2.1 if yes: how many times SINCE MOYO is weight plotted on growth chart

77 = n/a (no passport)

6) ANY RECURRENCE MALNUTRITION IN * *LAST 1 YEAR* ***?** *(or since MOYO disch if died)*

(NB Includes repeat admissions to MOYO since ORIGINAL EPISODE and/or MALNUTRITION AT DEATH)

6.1 ***TOTAL episodes of KWASHIORKOR / swelling =***		99 = DK
6.2 ***TOTAL episodes of MARASMUS / getting thin =***		99 = DK

If any episodes of repeat malnutrition:

	0 = no	1 =yes	77 = n/a	99 = DK
Did child go for medical (clinic/hospital) attention?				
How many times admitted to NRU (inpatient admission)			77 = n/a	99 = DK
How many times had CTC (RUTF/OTP only)			77 = n/a	99 = DK
How many times given advice / multivits / other *(circle)* ***-but NO RUTF***			77 = n/a	99 = DK
How many times referred to SFP programme alone			77 = n/a	99 = DK

Brief details - as relevant (e.g was child readmitted to MOYO or other NRU/ which OTP was doing CTC):

7) INPATIENT ADMISSIONS * LAST 1 YEAR ***** *(NOT SAM)* ? number, # | | 99 = DK

BRIEF details of Dx / Rx *(or between MOYO d/c and death if died)*

8) OUTPATIENT VISITS * LAST 6 MONTHS ***** *(NOT SAM)?* number, # | | 99 = DK

NB non-routine visits only - not ARV, OTP clinics *(or between MOYO d/c and death if died)*

9) CLINICAL PROGRESS / VERBAL AUTOPSY (*2 week history OR 2 weeks prior death if died*)

IN THE PREVIOUS ***2 WEEKS***, (BEFORE TODAY *OR* in 2/52 ***PRIOR TO DEATH*** IF DIED) did the child have:	**# days had problem** 0-14 days	**WHERE (if anywhere) did child get treatment in these 2 weeks?** (circle all that apply)	**Details of treatment:** (circle all that apply) ***(NOT incl. those given today)***
9.1 Fever		0 = none 1 = continued long standing treatment (e.g TB, COTRIM, ARV) 2 = inpatient admission 3 = outpatient clinic 4 = pharmacy 5 = shop / market 6 = relative / friend 7 = traditional healer 8 = other 99 = DK	1 = antibiotic 2 = antimalarial (SP/quinine) 3 = antipyretic (paracetamol / brufen etc) 4 = other / cannot say what 5 = ORS 99 = DK
9.2 Diarrhoea (≥ 3 **abnormally loose or watery** stools/24h)			
9.3 Vomiting			
9.4 Fast / Difficult breathing (chest problem~*WITH* **OR** *WITHOUT* cough)			
9.5 Cough (but ***NO*** fast or difficult breathing)			
9.6 Swelling (oedema)			
9.7 Other (1)			

REFER BACK TO MOYO / QECH IF SICK

10) TB medication

10.1 TB ever?	0 = no	1 = pre-MOYO	2 = started on MOYO ward /OTP			3 = start after MOYO OTP	99=DK
10.2 How many months did child have treatment for?	# months					77 = *n/a*	99=DK
10.3 If TB, were other children in family screened or treated				0 = no	1 = yes	77 = *n/a*	99 =DK

10.4 "Any problems with the treatment?" and/or "Why did child not have full 6 months treatment"

0 = no problems	30 = died<6m	31 = still taking					99 = DK

Describe problem:

11) SFP

11.1 How many months did child attend SFP for? (1 visit only=0.5m)	# months	99=DK
11.2 Which SFP did child go to (if did not go, which was nearest)		

11.3 "Any problems with the treatment?" ***and/or*** "Why did child not have full 4 months SFP"

0 = no problems	30 = died<4m	32=not referred					99 = DK

Describe problem:

12) COMMUNITY FOOD RATIONS (*other than SFP*) *** in your area *** in past year *** ?

12.1 Aside from SFP (above), were any other organizations offering food rations in your area?

0 = no, not aware of any	2 = yes, available, went, & told that child not eligible
1 = yes, food is available but child did not go	3 = yes, available, went AND received food

13) ACTIVITY LEVEL (usual - before illness that led to death if died)

3 = normal	2=some restriction	1=minimal activity	0=in bed all day	99=DK

14) FEEDING PRACTICES

14.1 Is (oe was) child still breast feeding?	1 = yes (in last 24hrs)	0 = no	If NO: age when stopped:			99 = DK
14.2 Did you attend any health / nutrition education sessions whilst on MOYO				0 = no	1 = yes	99 = DK
14.3 Did you feed your children differently after being on MOYO?				0 = no	1 = yes	99 = DK

if yes, describe (no prompts):

14.4 How many food groups are there? ____ *name them (circle each group named - no prompts)*

1=chakudya chokhutitsa? 2=chakudya chochokera ku nyama? 3=mafuta? 4=zipatso? 5=masamba?6=gulu la nyemba // 99=knows none

14.5 ***What Breast Feeding advice would you give to a new mother in your area:*** *99 = DK / cannot say*

~ Babies can be given other ***liquids*** (e.g water, teas, juices) *alongside* BF from ~			months
~ Babies can be given other ***solid*** foods (e.g porridge, nsima) *alongside* BF from ~			months
~ Ideally,a baby should BF until he/she is: _____years _____ months	66=as long as possible		99 = DK
~ If a mother is HIV +ve, when should she stop to BF her child completely?			
0 = should not BF at all	stop:	years	months

15) HIV STATUS

15.1 Child HIV status (see from old notes or passport)	0 = NON-R	1= R	2=not tested	
15.2 Is carer aware of the child's HIV status	0 = no	1 =yes	77 = not applicable e.g temporary carer / neighbour answering now	
15.3 Is a Re-test needed:	0 = no	1 = yes: see flowchart+say why:		
if yes:	1 = Retest done, still R	2 = retest done, NR	3 = counselled & referred now	99=DK

NB IF carer unaware of status, see status in notes/passport and counsel appropriately / refer back to VCT

IF HIV (R):

16) COTRIMOXAZOLE PROPHYLAXIS *(should be ONE DAILY dose)*

circle ALL that apply

16.1 CoT ever?	0 = never	1 =start pre-MOYO	2 = started on MOYO ward /OTP	3 = start after MOYO OTP	99=DK

16.2 When did child LAST take a dose of CoT *(NB short TREATMENT courses from health centre do no count)*

0=today	1=yesterday	2 = Dzana (two days ago)	3 = three to seven days ago	4 = one week to one month ago	5 = more than 1 month ago	6=never since MOYO OTP	99 = DK

16.3 Where got CoT from? (after MOYO OTP)	1=CoT clinic, QECH	2 = Health centre (which:)	3 = Other (where):	77 = n/a (never took)	99 = DK

16.4 **"Any problems taking DAILY cotrim prophylaxis"** (see codes, list all that apply)

0 = no problems							99 = DK

DETAILS

17) ARV medication *(should be two DAILY doses)*

circle ALL that apply

17.1 On ARV?	0 = never	1 =start pre-MOYO	2 = started on MOYO ward /OTP	3 = start after MOYO OTP	99=DK
	4 = not yet eligible: *(say why not)*				

17.2 If *EVER* ARV: Date started: _____dd/_____mm/ ____yy TO:	still taking now / at death	date stopped / /		
17.3 If *EVER* ARV: where	1 = QECH	2 = health centre (which:)	77=n/a	99 = DK

17.4 When did child ***LAST TAKE*** his/her ARV medication?

0=today	1=yesterday	2 = Dzana (two days ago)	3 = three to seven days ago	4 = one week to one month ago	5 = more than 1 month ago	6=never since MOYO OTP	77 = n/a 99 = DK

17.5 When did your child *last* miss a dose (tick one box only)

1 = missed within last week	2 = missed dose 1-2 weeks ago	3=missed dose 2-4 weeks ago	
4=missed dose 1-3months ago	5=missed nothing last 3/12	77=n/a (stopped/not taking)	99 - DK

17.6 "What problems were there (MUST be problem if missed dose/not taken today)" (see codes, list all that apply)

0 = no problems							99 = DK

DETAILS

18) *Has home address changed?*

0 = no, as before	1 = yes: get new details	99 = moved but ?where

19) EXTRA NOTES / ACTION FOLLOWING 1 YEAR FOLLOW-UP VISIT (Give details where relevant)			
0=no action needed	1=advice: 1a) general nutrtion advice 1b) other	2=refer to outpatient service:	3=readmit to MOYO/QECH

Date ____d/____m/200_ **Interviewer initials**

G.2 Anthropometry (including sibling anthropometry and clinical status)

Page 5/6 **MOYO 1 YEAR follow-up:** ***INDEX CHILD*** **HMIS no:**

INITIALS

MOYO 1 year follow-up ~ Family Clinical

		Basic details				**anthropometry**				**clinical progress** (current, or before death if died)	
		sex	***DOB***	***Age now***	***How now?***	**Weight**	**MUAC**	**length or height**	WHICH MEASURED: h=height; l=length	**Ever** kwash or marasmus	**Notes/ details**
		1 = male / 2=female	(dd/mm/yy)	(or age of death if died	0 = died 1=alive,well 2=alive,ill 99=DK	(kg)	(cm)	(cm)		0=never 1=NRU admission 2=CTC 3=multivit/ drugs only 4=advice only 5=nil Rx, 6=SFP	details of any SAM / inpatient / why died if died --- (Diagnosis, dates)
1	1stborn										
2	2ndborn										
3	3rdborn										
4	4thborn										
5	5thborn										
6	6thborn										
7	7thborn										
8	lastborn										

DRAW ARROW ---> to idenitfy birth order of MOYO sib

continue on separate sheet if needed

G.3 HIV status and testing

Page 6/6 **MOYO 1 YEAR follow-up:** Y06___ ***index child*** HMIS no: | INITIALS

MOYO 1 year follow-up ~ FAMILY HCT TESTS

		any PMTCT @ birth? 0=no 1=HIV test for mum only 2=HIV test mum+baby 3=HIV test+single dose ARV drug 4=other 99=dk.	***Tested for HIV?*** **REPORTED:** 0=tested~NR --- 1=tested~R --- 2=never tested --- 99=DK	***Tested (stamp)*** **PASSPORT:** 0=NR stamp ---- 1=R stamp ---- 2=no stamp seen ---- 3=passport n/a	***If tested, when*** 1=pre-MOYO --- 2=@MOYO --- 3=after MOYO D/C	**If *not* tested** **WHY NOT? (see code sheet)** + write in "NOTES"	**if tested (R) IS (or WAS) the family member:** **On COT?** 0=never 1=occ 2=daily 3=was taking, but now stopped	**On ARV ?** 0=no ----- 1=yes -------- 2=waiting list ------ 3=not eligible ------ 4=started, but now stopped	**Notes** e.g. details of PMTCT / reason for not testing - if unable to code accurately ~~~~ also document any differences between test result reported and that written in passport ~~~~~ when MOTHER started ARV if she is taking
4.1	Mother								
4.2	Father								
4.3	Carer (if not mum or dad)								
4.4	1stborn								
4.5	2ndborn								
4.6	3rdborn								
4.7	4thborn								
4.8	5thborn								
4.9	6thborn								
4.10	7thborn								
4.11	lastborn								

DRAW ARROW ---> to idenitfy birth order of MOYO sib

NB WHY NOT ~ write in text AND (if possible) code from sheet

Annex H FUSAM study additional details and results

H.1 Baseline patient profile at admission to MOYO

H.1.1 Subtype of wasting

Table 46 Subtypes of wasting showing those who were wased according to low MUAC only or low WHM only – by HIV status

	All admissions ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at >1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Severe wasting (all)	275/1024 (27%)	135/322 (42%)	55/105 (52.4%)	69/462 (15%)	16/135 (12%)
Wasting (MUAC <11cm only)	122/1024 (12%)	49/322 (15.2%)	32/105 (30.5%)	32/462 (7%)	9/135 (7%)
HIV ⊖	*29/459 (6%)*	*7/57 (12%)*	*3/20 (15%)*	*19/315 (6%)*	*0*
HIV ⊕	*81/445 (18%)*	*33/191 (17%)*	*29/83 (35%)*	*13/139 (9%)*	*6/32 (19%)*
HIV unknown	*12/120 (10%)*	*9/74 (12%)*	*0*	*0*	*3/36 (8%)*
Wasting (WHM <70% only)	13/1024 (1%)	7/322 (2%)	2/105 (2%)	4/462 (1%)	0/135 (0%)
HIV ⊖	*2/459 (0.4%)*	*1/57 (2%)*	*1/20 (5%)*	*0*	*0*
HIV ⊕	*9/445 (2%)*	*5/191 (3%)*	*1/83 (1%)*	*3/139 (2%)*	*0*
HIV unknown	*2/120 (2%)*	*1/74 (1%)*	*0*	*1/8 (13%)*	*0*

H.1.2 Malnutrition severity at admission - details

Admission anthropometry stratified by SAM type and by hiv status is shown in **Table 13**. As expected, weight-for-height is lowest among wasted patients and those who are HIV seropositive. Overall and in children with oedematous malnutrition, it is also lower in deaths than in those still alive at 1 year. Unknown final outcomes are more similar to those known alive than to deaths. Similar patterns are seen for weight-for-age and height-for-age z-scores.

Table 47 Weight-for-height, weight-for-age and height-for-age at admission – by SAM type and HIV status

	All admissions ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at >1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Weight-for-height	**-2.25 (1.3)**	***-2.77 (1.2)***	***-2.65 (1.2)***	***-1.92 (1.2)***	***-1.86 (1.3)***
Oedematous patients	**-1.89 (1.2)**	*-2.39 (1.2)*	*-2.22 (1.4)*	*-1.68 (1.1)*	*-1.67 (1.2)*
Wasted patients	**-3.20 (0.9)**	*-3.23 (1.0)*	*-3.06 (0.8)*	*-3.27 (0.8)*	*-3.10 (1.2)*
in HIV ⊖	**-1.87 (1.2)**	*-2.56 (1.2)*	*-2.08 (1.6)*	*-1.81 (1.2)*	*-1.49 (1.3)*
in HIV ⊕	**-2.59 (1.2)**	*-2.85 (1.2)*	*-2.82 (1.0)*	*-2.16 (1.3)*	*-2.35 (1.2)*
in HIV unknown	**-2.60 (1.2)**	*-2.72 (1.2)*	*-1.55 (1.2)*	*-2.37 (1.2)*	*-2.36 (1.2)*
Weight-for-age	**-3.59 (1.3)**	***-4.13 (1.1)***	***-4.30 (1.1)***	***-3.18 (1.2)***	***-3.14 (1.4)***
Oedematous patients	**-3.15 (1.2)**	*-3.67 (1.1)*	*-3.73 (1.3)*	*-2.91 (1.1)*	*-2.85 (1.3)*
Wasted patients	**-4.71 (0.7)**	*-4.73 (0.7)*	*-4.79 (0.7)*	*-4.61 (0.6)*	*-4.82 (0.7)*
in HIV ⊖	**-3.09 (1.3)**	*-3.86 (1.1)*	*-3.74 (1.6)*	*-3.00 (1.2)*	*-2.66 (1.3)*
in HIV ⊕	**-4.02 (1.1)**	*-4.21 (1.1)*	*-4.45 (0.9)*	*-3.58 (1.2)*	*-3.71 (1.0)*
in HIV unknown	**-4.00 (1.3)**	*-4.13 (1.2)*	*-3.86 (0.2)*	*-3.28 (1.8)*	*-3.83 (1.6)*
Height-for-age	**-3.23 (1.4)**	***-3.43 (1.4)***	***-3.88 (1.3)***	***-3.03 (1.4)***	***-2.94 (1.5)***
in HIV ⊖	**-2.90 (1.4)**	*-3.16 (1.4)*	*-3.68 (1.6)*	*-2.86 (1.4)*	*-2.66 (1.5)*
in HIV ⊕	**-3.58 (1.3)**	*-3.54 (1.3)*	*-3.93 (1.2)*	*-3.44 (1.3)*	*-3.50 (1.3)*
in HIV unknown	**-3.27 (1.7)**	*-3.36 (1.5)*	*-3.97 (0.0)*	*-2.86 (2.6)*	*-3.02 (1.9)*

H.1.3 HIV profile

Table 48 Baseline HIV profile

	All admissions ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at >1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Child HIV status					
HIV ⊖	**459 (45%)**	*57 (18%)*	*20 (19%)*	*315 (68%)*	*67 (50%)*
HIV ⊕	**445 (43%)**	*191 (59%)*	*83 (70%)*	*139 (30%)*	*32 (24%)*
HIV unknown	**120 (12%)**	*74 (23%)*	*2 (2%)*	*8 (2%)*	*36 (27%)*
HIV staging: *HIV ⊖* ***only***	**n=440**	*n=52*	*n=20*	*n=307*	*n=61*
Stage 0	**112 (25%)**	*7 (14%)*	*3 (15%)*	*86 (28%)*	*16 (26%)*
Stage 1 or 2	**69 (16%)**	*6 (12%)*	*5 (25%)*	*51 (17%)*	*7 (11%)*
Stage 3	**197 (45%)**	*35 (67%)*	*8 (40%)*	*129 (42%)*	*25 (41%)*
Stage 4	**62 (14%)**	*4 (8%)*	*4 (20%)*	*41 (13%)*	*13 (21%)*
HIV staging: *HIV ⊕* ***only***	**n=431**	*n=185*	*n=83*	*n=134*	*n=29*
Stage 0	**44 (10%)**	*14 (8%)*	*9 (11%)*	*19 (14%)*	*2 (7%)*
Stage 1 or 2	**57 (13%)**	*21 (11%)*	*6 (7%)*	*26 (19%)*	*4 (14%)*
Stage 3	**235 (55%)**	*101 (55%)*	*53 (64%)*	*65 (49%)*	*16 (55%)*
Stage 4	**95 (22%)**	*49 (27%)*	*15 (18%)*	*25 (18%)*	*7 (24%)*
CD4*	**n=208**	*n=31*	*n=63*	*n=93*	*n=21*
CD4 severely low (age adjusted %)	**126 (61%)**	*27 (87%)*	*40 (63%)*	*45 (48%)*	*14 (70%)*
CD4%, mean (SD)	**17.9 (9.8)**	*12.9 (8.4)*	*17.1 (8.2)*	*20.5 (10.6)*	*16.3 (9.5)*

H.1.4 Clinical profile

Table 49 Baseline clinical profile in full

	All admissions ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at >1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Symptoms in previous 2 weeks					
Any	**959/980 (98%)**	*309/311 (99%)*	*102/105 (97%)*	*447/460 (97%)*	*101/104 (97%)*
Fever	**637/979 (65%)**	*205/311 (66%)*	*73/104 (70%)*	*293/458 (64%)*	*66/106 (62%)*
Diarrhoea	**647/977 (66%)**	*231/310 (75%)*	*72/105 (69%)*	*280/456 (61%)*	*64/106 (60%)*
Vomiting	**450/982 (46%)**	*163/313 (52%)*	*42/105 (40%)*	*203/458 (44%)*	*42/106 (40%)*
Abdominal pain	**377/923 (41%)**	*123/269 (46%)*	*37/104 (36%)*	*188/452 (42%)*	*29/98 (30%)*
Fast or difficult breathing	**143/970 (15%)**	*45/303 (15%)*	*20/104 (19%)*	*62/457 (14%)*	*16/106 (15%)*
Cough	**580/977 (59%)**	*193/308 (63%)*	*76/105 (72%)*	*254/459 (55%)*	*57/105 (54%)*
Anorexia	**503/953 (53%)**	*169/294 (57%)*	*51/104 (49%)*	*230/454 (51%)*	*53/101 (52%)*
Flaky paint dematosis	**174/967 (18%)**	*49/306 (16%)*	*14/104 (13%)*	*89/452 (20%)*	*22/105 (21%)*
Other	**238/977 (24%)**	*84/314 (27%)*	*34/104 (33%)*	*101/454 (22%)*	*19/105 (18%)*
Outpatient consultations in 2 weeks prior to admission (any)					
Any	**658/928 (71%)**	*204/271 (75%)*	*68/102 (67%)*	*318/456 (70%)*	*68/99 (69%)*
Medication use in 2 weeks prior to admission					
Any	**843/951 (89%)**	*264/296 (89%)*	*95/103 (92%)*	*394/450 (88%)*	*90/102 (88%)*
Anaemia					
Any (PCV<30)	**320/914 (35%)**	*103/294 (35%)*	*39/96 (41%)*	*141/424 (33%)*	*37/100 (37%)*
Severe (PCV <15)	**18/914 (2%)**	*11/294 (4%)*	*1/96 (1%)*	*5/424 (1%)*	*1/100 (1%)*
Malaria (+ve thick blood film on admission)	**37/898 (4%)**	*9/292 (3%)*	*3/94 (3%)*	*21/415 (5%)*	*4/97 (4%)*
Has traditional medicine amulet or charm	**245/905 (27%)**	*87/266 (32%)*	*25/100 (25%)*	*108/444 (24%)*	*25/95 (26%)*
Breastfed (<2 year olds only)	**253/557 (45%)**	*102/192 (53%)*	*47/69 (68%)*	*79/243 (33%)*	*25/53 (53%)*
Disability (any)	**60/938 (6%)**	*24/282 (9%)*	*9/102 (9%)*	*22/453 (5%)*	*5/101 (5%)*

H.1.5 Past medical history

Table 50 Past medical history in full

	All admissions ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at >1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Past inpatient and outpatient episodes (any)					
Inpatient admissions *(non-SAM, in past year)*	**190/931 (20%)**	*88/283 (31%)*	*22/102 (22%)*	*69/444 (16%)*	*11/102 (11%)*
Inpatient admissions *(for SAM, ever)*	**134/939 (14%)**	*47/282 (17%)*	*15/102 (15%)*	*57/452 (13%)*	*15/103 (15%)*
Outpatient episodes *(last 6 months)*	**797/884 (90%)**	*233/253 (92%)*	*90/98 (92%)*	*396/440 (90%)*	*78/93 (84%)*
Outpatient episodes *(last 6 months,* ***with symptoms suggestive of malnutrition)***	**187/882 (21%)**	*60/254 (24%)*	*26/97 (27%)*	*84/437 (19%)*	*17/94 (18%)*
Outpatient episodes *(for SFP, ever)*	**203/910 (22%)**	*62/267 (23%)*	*29/102 (28%)*	*93/445 (21%)*	*19/96 (20%)*
Ex Low Birth weight (reported by carer)	**86/899 (10%)**	*29/257 (11%)*	*13/98 (13%)*	*39/449 (9%)*	*5/95 (5%)*
Ever had TB	**32/924 (3%)**	*15/273 (5%)*	*4/103 (4%)*	*10/450 (2%)*	*3/98 (3%)*
Ever had measles vaccine	**808/937 (86%)**	*232/290 (80%)*	*81/98 (82%)*	*401/448 (90%)*	*94/101 (93%)*

H.1.6 Family profile

Table 51 Family profile in full table

	All admissions ***(n=1024)***	*Inpatient or OTP death* *(n=322)*	*Late death* *(n=105)*	*Alive at >1 year post admission* *(n=462)*	***Unknown 1 year outcome*** ***(n=135)***
Orphan					
Mother died	**72/916 (8%)**	*18/264 (7%)*	*10/102 (10%)*	*36/457 (8%)*	*8/93 (9%)*
Father died	**64/908 (7%)**	*22/261 (8%)*	*9/102 (9%)*	*28/452 (6%)*	*5/93 (5%)*
Both dead	**24/823 (3%)**	*9/240 (4%)*	*4/91 (4%)*	*10/410 (2%)*	*1/82 (1%)*
Previous child death in family	**233/970 (24%)**	*76/306 (25%)*	*24/103 (23%)*	*110/457 (24%)*	*23/104 (22%)*
Birth order of MOYO child					
First	**257/925 (28%)**	*76/272 (28%)*	*26/103 (25%)*	*126/453 (28%)*	*29/97 (30%)*
Second	**242/925 (26%)**	*70/272 (26%)*	*26/103 (25%)*	*115/453 (25%)*	*31/97 (32%)*
Third	**188/925 (20%)**	*60/272 (22%)*	*20/103 (19%)*	*87/453 (19%)*	*21/97 (22%)*
Fourth or later	**238/925 (26%)**	*66/272 (24%)*	*31/103 (30%)*	*125/453 (28%)*	*16/97 (16%)*
Maternal education					
None	**101/876 (12%)**	*30/254 (12%)*	*13/98 (13%)*	*51/433 (12%)*	*7/91 (8%)*
Primary school	**605/876 (69%)**	*164/254 (65%)*	*70/98 (71%)*	*303/433 (70%)*	*68/91 (74%)*
Secondary school	**170/876 (19%)**	*60/254 (24%)*	*15/98 (15%)*	*79/433 (18%)*	*16/91 (18%)*
Paternal education					
None	**27/652 (4%)**	*10/176 (6%)*	*1/68 (1%)*	*14/337 (4%)*	*2/71 (3%)*
Primary school	**297/652 (46%)**	*77/176 (44%)*	*31/68 (46%)*	*156/337 (46%)*	*33/71 (47%)*
Secondary school	**328/652 (50%)**	*89/176 (51%)*	*36/68 (53%)*	*167/337 (50%)*	*36/71 (51%)*
Mother illiterate	**315/885 (36%)**	*88/256 (34%)*	*35/100 (35%)*	*160/437 (37%)*	*32/92 (35%)*
Father illiterate	**77/838 (9%)**	*25/233 (11%)*	*5/93 (5%)*	*36/423 (9%)*	*11/89 (12%)*

H.1.7 Socioeconomic profile

Table 52 Socioeconomic profile and residence details in full

	All admissions (n=1024)	*Inpatient or OTP death (n=322)*	*Late death (n=105)*	*Alive at >1 year post admission (n=462)*	***Unknown 1 year outcome (n=135)***
Mother's occupation					
Housewife	**479/1024 (47%)**	*135/322 (42%)*	*55/105 (52%)*	*242/462 (52%)*	*47/135 (35%)*
Ganyu	**157/1024 (15%)**	*44/322 (14%)*	*16/105 (15%)*	*81/462 (18%)*	*16/135 (12%)*
Employee/ self employed	**208/1024 (20%)**	*63/322 (20%)*	*25/105 (24%)*	*95/462 (21%)*	*25/135 (19%)*
Other or unknown	**180/1024 (18%)**	*80/322 (25%)*	*9/105 (9%)*	*44/462 (10%)*	*47/135 (35%)*
Father's occupation					
Unemployed	**211/1024 (21%)**	*76/322 (24%)*	*17/105 (16%)*	*66/462 (14%)*	*52/135 (39%)*
Ganyu	**155/1024 (15%)**	*38/322 (12%)*	*17/105 (16%)*	*86/462 (19%)*	*14/135 (10%)*
Employee/self employed/other or unknown	**658/1024 (64%)**	*208/322 (65%)*	*71/105 (68%)*	*310/462 (67%)*	*69/135 (51%)*
Rural residence	**331/898 (37%)**	*82/256 (32%)*	*34/99 (34%)*	*191/451 (42%)*	*24/92 (26%)*
Admitted to MOYO:					
Direct to MOYO or readmission	**285/856 (33%)**	*90/244 (37%)*	*35/98 (36%)*	*124/427 (29%)*	*36/87 (41%)*
Via other QECH paediatric ward	**56/856 (7%)**	*22/244 (9%)*	*10/98 (10%)*	*21/427 (5%)*	*3/87 (3%)*
Referred from other clinic	**515/856 (60%)**	*132/244 (54%)*	*53/98 (54%)*	*282/427 (66%)*	*48/87 (55%)*
Wealth quintile					
Poorest	**169/845 (20%)**	*43/240 (18%)*	*17/95(18%)*	*97/426 (23%)*	*12/84 (14%)*
2nd poorest	**169/845 (20%)**	*49/240 (20%)*	*14/95 (15%)*	*92/426 (22%)*	*14/84 (17%)*
Middle	**169/845 (20%)**	*44/240 (18%)*	*23/95 (24%)*	*82/426 (19%)*	*20/84 (24%)*
2nd richest	**169/845 (20%)**	*50/240 (21%)*	*15/95 (16%)*	*83/426 (19%)*	*21/84 (25%)*
Richest	**169/845 (20%)**	*54/240 (23%)*	*26/95 (27%)*	*72/426 (17%)*	*17/84 (20%)*
Main household water source					
Piped	**502/913 (55%)**	156/264 (59%)	59/101 (58%)	227/455 (50%)	60/93 (65%)
Borehole	**300/913 (33%)**	74/264 (28%)	29/101 (29%)	177/455 (39%)	20/93 (22%)
Well or spring	**111/913 (12%)**	34/264 (13%)	13/101 (13%)	51/455 (11%)	13/93 (14%)
Main household toilet					
Flush toilet	**22/913 (2%)**	5/264 (2%)	4/101 (4%)	12/455 (3%)	1/93 (1%)
Traditional pit (own)	**345/913 (38%)**	110/264 (42%)	30/101 (30%)	179/455 (39%)	26/93 (28%)
Traditional pit (shared)	**538/913 (59%)**	148/264 (56%)	67/101 (66%)	259/455 (57%)	64/93 (69%)
Bush toilet or other	**8/913 (1%)**	1/264 (0.4%)	0/101 (0%)	5/455 (1%)	2/93 (2%)

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K.2 Latest version of the MOYO chart, as field tested in Ethiopia, 2009

(1st Prize Poster, Royal Society of Tropical Medicine "Research in Progress" meeting, December 2009)

Evaluating the Moyo chart – a novel, low-cost, weight-for-height slide chart for the improved assessment of nutritional status in children

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Background

- The 'Moyo' chart, developed in Malawi, is a simple, low-cost tool for the assessment of nutritional status in children. Correct diagnosis is a critical first step on the path towards treatment and recovery.
- Anecdotal evidence suggests that the Moyo chart is easier to use, quicker and more accurate than traditional weight-for-height 'look-up' tables.
- Formal evaluation is important prior to a planned roll-out of the Moyo chart, in collaboration with TALC (Teaching Aids at Low Cost).
- In this study carried out in June 2009, we explore the hypothesis that the Moyo chart improves the speed, accuracy and ease of nutritional assessment.

Methods

Study Design:

- A cross-over RCT using the Moyo chart and look-up tables.

Participants:

- 61 junior medical students at the University of Addis Ababa received equal training in the use of each tool (students were asked about any relevant prior experience).

Randomisation and blinding:

- An allocation sequence was randomly generated and concealed using sealed envelopes. One group received a Moyo chart for the first examination time block of 12 minutes, the other a look-up table. Participants then swapped tools and were given a new set of cases to diagnose for the second time block.
- It was not possible to blind participants to the tool used, but the precise research hypothesis was not revealed.
- Results were marked by CS, who was also not blind to the assessment tool being used. We do not believe this introduced any important bias as the measurement scale is objective.

Measurement of accuracy and speed of use:

A written examination was undertaken by participants, classifying hypothetical cases as normal, severely or moderately malnourished.

Outcomes:

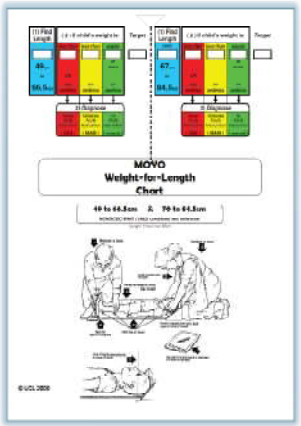
Primary i) '% diagnostic accuracy' = proportion of total diagnoses which were correct

ii) 'time per correct diagnosis' (seconds)

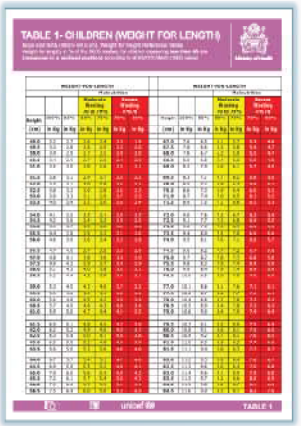
Secondary iii) perceived ease and speed of use and acceptability, assessed by participant survey

Analysis:

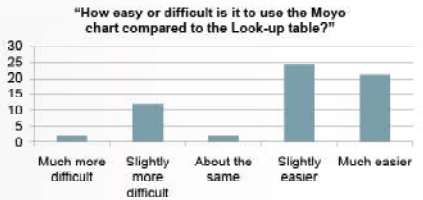
Paired t-test, using SPSS v18 (© SPSS inc. USA).

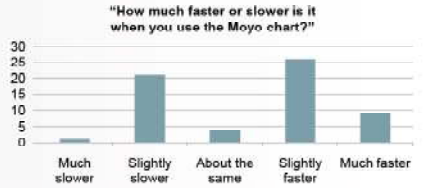


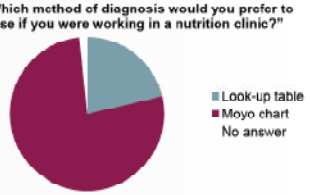
The Moyo chart



The look-up table







Results

		Moyo chart	Look-up table	Difference	P value
Percentage accuracy (%)	Mean (95% CI)	83.2 (77.7 - 88.8)	76.1 (71.2 - 81.0)	7.1 (1.7 - 12.5)	p = 0.011
	Range	(0.0 - 100.0)	(10.0 - 100.0)		
Accurate time (s)	Mean (95% CI)	42.5 (32.2 - 52.8)	56.4 (33.3 - 79.5)	-13.1 (-35.7 - 9.4)	p = 0.248
	Range	(14.4 - 240.0)	(16.0 - 720.0)		

Collaborators

Addis Ababa University www.aau.edu.et

TALC Teaching-aids At Low Cost www.talcuk.org

Emergency Nutrition Network www.ennonline.net

Funded by UCL Futures

Conclusions

- Preliminary results show that the Moyo chart is a more accurate diagnostic method for nutritional assessment than traditional look-up tables. The 7.1% increase in diagnostic accuracy could be clinically important as well as statistically significant.
- Accurate diagnoses of nutritional status were made more quickly using the Moyo chart than the look-up table. Though not statistically significant due to wide confidence intervals, any time saved could be clinically relevant in a busy child health or nutrition outpatient setting.
- The MOYO chart is easy to use and acceptable. In this study of participants naïve to nutritional assessment methods, the MOYO chart was both preferable to and easier to use than a traditional look-up table.
- Further analysis and feedback will be used to finalise the chart's format. We believe that a roll-out of the chart is worthwhile and could aid the diagnostic work of frontline health and nutrition workers.

Mural: Mua Mission, Malawi

"They shall neither hunger anymore, nor thirst anymore;"

Revelation 7:16