Simplified, combined protocol for acute malnutrition in children 6-59 months: the ComPAS randomized controlled trial

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Declaration

I, Jeanette Bailey, 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 in the thesis.

Signed: Jeanette Bailey

Date: 1 April 2021

Abstract

Background

Children 6-59 months with uncomplicated severe and moderate acute malnutrition (SAM and MAM) are treated in separate programs with different food products. The aim of this research was to generate evidence on a simplified, combined SAM and MAM approach, using a mid-upper arm circumference (MUAC)-based dosage protocol.

Methods

An analysis of routine program data of 5,518 children from five countries estimated the energy requirements of children recovering from acute malnutrition to develop a MUAC-based combined protocol. A cluster-randomized controlled trial in Kenya and South Sudan tested if the combined protocol was as effective at recovering children but more cost-effective than standard treatment. A secondary analysis explored outcomes in children with low weight-for-age (WAZ <-3.0) and/or MUAC <11.5 cm.

Results

In the routine program analysis, energy requirements for children with a MUAC <12.5 cm could be met or exceeded by 1,000 kcal/day. In the trial, 2,488 children completed treatment; 981 (76.3%) on the combined protocol and 884 (73.5%) on the standard protocol recovered. The combined protocol was non-inferior to standard treatment at a 10% non-inferiority margin, with a risk difference of 0.03 (95% CI -0.05 to 0.10, p=0.52) in per-protocol analysis, adjusted for country, age and sex. The amount of ready-to-use food to fully recover a child admitted with SAM was less in the combined protocol (122 versus 193 sachets), and the combined protocol cost $123 less per child recovered ($918 vs 1,041). Children with a WAZ <-3.0 or a MUAC <11.5 cm respond similarly to the combined protocol or standard treatment.

Conclusion

A simplified, combined protocol for SAM and MAM achieves similar recovery as standard treatment and improves cost-effectiveness. Improving cost-effectiveness may enable health programs to treat more children. Adding WAZ <-3 as an admission criterion to simplified programs may help target high-risk children who benefit from treatment.

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Preface and Acknowledgments

When I began this research, I was working as a nutrition advisor at the International Rescue Committee (IRC) in New York City. I spent the prior decade living mostly overseas- with a year in London completing my MSc at LSHTM- and the rest primarily in Latin America, Africa and Asia working in nutrition programs with Action Against Hunger (AAH), Save the Children and Médecins Sans Frontières (MSF). In January 2014 I was sitting in a meeting of nutrition advisors from various UN and NGO's and listening to colleagues share recent research. As I looked at graphs depicting weight and MUAC gain in the early weeks of treatment, it struck me how the line between severe and moderate acute malnutrition (SAM and MAM) was largely arbitrary. It seemed inefficient to organize programming this way- with different protocols, food products and programs to treat SAM and MAM. In my own field experience, I had rarely seen programs that had the time or resources to set up both SAM and MAM treatment in the early stages of an emergency. I observed frustrated parents turned away from feeding programs because their children barely missed the admissions cut-offs. They would return to their communities where aggravating factors often caused their moderately malnourished children to deteriorate. Many eventually returned with a much sicker child who had developed SAM, now eligible for treatment but at a higher risk of death and long-term health consequences. Once they developed SAM, these children required much more intensive intervention, with systematic medications, greater quantities of therapeutic food and sometimes hospitalization.

I had seen enough to know the system was not working well. I walked to the flip chart at the front of the room and drew a few lines across the page. I asked my colleagues to forget about SAM and MAM for a moment and just think about a spectrum of severity, correlated with rate of growth and energy needs as children progress through treatment (Figure 1).

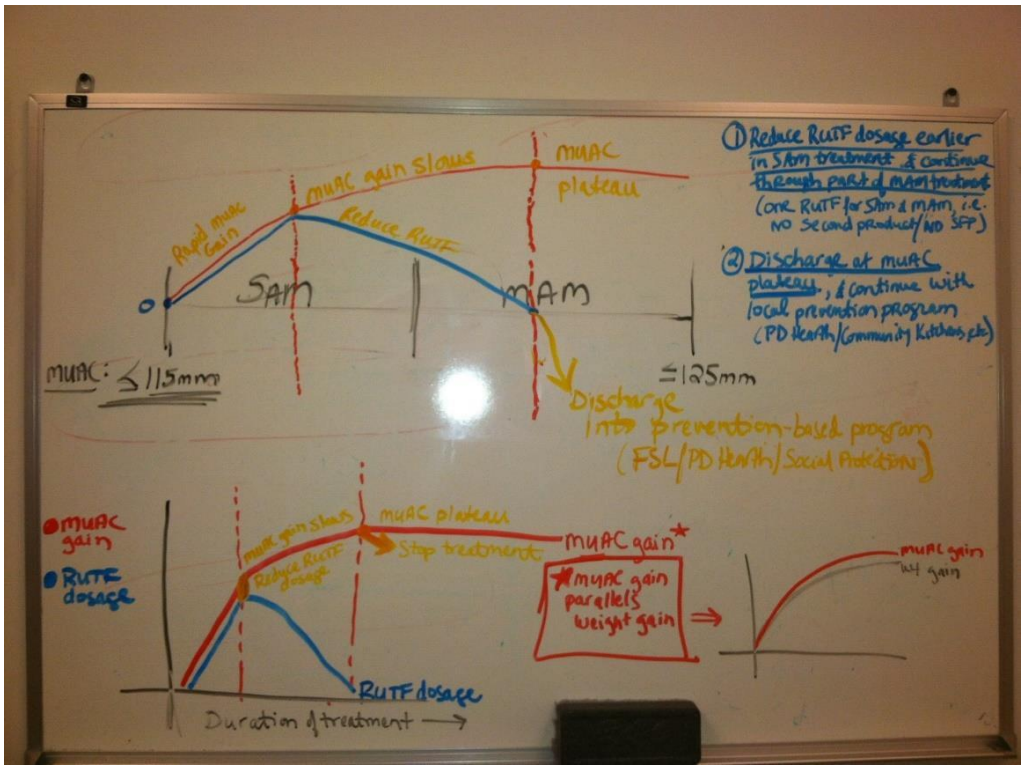

Figure 1: Drawing of initial research idea, February 2014

I looked back at my colleagues, waiting for their reaction. We talked at length about this continuum and what it means for programming. We were curious to know what would happen if we could simplify things, save money, and perhaps reach more children with similar resources- before they became severely malnourished.

This idea eventually became the Combined Protocol for Acute Malnutrition Study (ComPAS), a project that defined my work at the IRC from 2014-2021. After finding funding for the research and building a coalition of partners to support it, I registered as a PhD candidate in January 2016. ComPAS became a global research coalition of NGO's, academics, UN agencies and Ministries of Health.

With such a large coalition, there are too many people to even begin to thank, all of whom helped make ComPAS and my PhD research possible in different ways. To my colleagues and co-investigators across the IRC, AAH, MSF, No Wasted Lives, the Wasting Stunting Technical Interest Group, Office of U.S. Foreign Disaster Assistance (OFDA), Children's Investment Fund Foundation (CIFF), United Nations Children's Fund (UNICEF), World Food Programme (WFP), Ministries of Health and beyond who reviewed drafts, gave advice, helped us find funding, designed tools, worked day-to-day treating children in the clinics, supervised data collection, and so much more- I am grateful to all of you. Thank you to Dr. Rachel Chase, Dr. Natasha Lelijveld and Dr. Mark Myatt for your close

collaboration and support with the various sub-studies of ComPAS. Thank you to my sponsor Action Against Hunger-UK for funding the first three years of my PhD fees. Special thanks to the Ministries of Health in Kenya and South Sudan for hosting the trial, and most of all to the children and their families who agreed to participate in this research.

To say I am grateful to my two PhD supervisors- Dr. Marko Kerac and Dr. Charles Opondo- is an understatement. They have been my mentors, my teachers, my colleagues, and an unwavering academic support team throughout the past 5 years. They were always available- even for daily calls and emails during the most intensive periods of the study. I often hear their words in my head, reminding me that every challenge is part of the process. They have helped me embrace the learning opportunities that each challenge presented.

Finally, thanks to my family. I started building ComPAS a few months before becoming pregnant with my first child, Aidan. Aidan traveled with me to London when I registered for the PhD in 2016 and wandered the halls of his mother's favorite institution, LSHTM. He attended nursery school in London in 2018 and even briefly acquired a British accent. My daughter Kiera arrived days after I submitted the trial results paper for peer-review in 2019. My children's early years were filled with milestones for my PhD as I grew into both a researcher and a mother. Thank you to Aidan and Kiera, and to my husband Brent- for being the love that keeps me going. Thank you to my mother and father, my two brothers, and my sister for always being excited about every new paper that is published. A special thanks to my sister Jacquelyn for traveling to London multiple times with Aidan and I to help with childcare while I worked on my PhD. Thank you to my father for his advice and stories of his own experience completing his PhD. I am grateful I did not have to re-type this thesis repeatedly on a typewriter like he did.

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Note: Figures and tables for each research paper are embedded within the PDF of the publication and not included in the list above.

List of Abbreviations

AAH	Action Against Hunger
ALIMA	Alliance for International Medical Action
CHW	Community health workers
CIFF	Children's Investment Fund Foundation
CMAM	Community-based management of acute malnutrition
ComPAS	Combined Protocol for Acute Malnutrition Study
COVID-19	Coronavirus disease 2019
CSB	Corn-soya blend
ECHO	European Civil Protection and Humanitarian Aid Operations
HAZ	Height-for-age z-score
IRC	International Rescue Committee
kcal	kilocalorie
KEMSA	Kenya Medical Supplies Agency
LNS	Lipid nutrient supplement
LSHTM	London School of Hygiene and Tropical Medicine
MAM	Moderate acute malnutrition
MoH	Ministry of Health
MSF	Médecins Sans Frontières
MUAC	Mid-upper arm circumference
NGO	Non-governmental organization
OFDA	Office of U.S. Foreign Disaster Assistance
RCT	randomized controlled trial
RUF	Ready-to-use food

RUSF	Ready-to-use supplementary food
RUTF	Ready-to-use therapeutic food
SAM	Severe acute malnutrition
SMS	Soya-maize-sorghum
UN	United Nations
UNHCR	United Nations High Commissioner for Refugees
UNICEF	United Nations Children's Fund
WAZ	Weight-for-age z-score
WFP	World Food Programme
WHO	World Health Organization
WHZ	Weight-for-height z-score

Chapter 1: Introduction

1.1 Background

1.1.1 Global landscape of childhood malnutrition

Childhood malnutrition is one of the world's greatest public health challenges. Malnutrition is a leading underlying cause of mortality and morbidity worldwide,[1] and contributes to nearly half of all deaths in children under five years of age.[2] Millions of children die every year when their bodies fail due to inadequate nutrition and the associated medical complications that develop as a result.[2] At any given time, approximately 50 million children experience acute malnutrition,[3] and the total numbers each year are likely much higher given this estimate is derived from prevalence surveys.[4-6] Government investments to address malnutrition do not meet the need. In 48 mainly low-income countries reporting health expenditures, nutrition received the lowest funding of any disease category.[1] Global and national nutrition data hides inequalities that become apparent only at the most localized level, with childhood malnutrition up to nine times higher in more vulnerable communities within the same country.[1] Climate change, conflict and global health crises have worsened existing inequities in food and health systems, slowing and even reversing progress to reduce global childhood malnutrition in some communities affected by poverty and conflict.[1, 7]

1.1.2 Defining acute malnutrition

Malnutrition has many forms, including acute malnutrition (wasting), chronic malnutrition (stunting), micronutrient deficiencies, underweight, overweight and obesity. Acute malnutrition in children, or wasting, has a high short-term fatality rate and long-term health consequences for those who survive.[8-10] Acute malnutrition in children 6-59 months is currently defined as:

- Severe acute malnutrition (SAM): weight-for-height <-3.0 standard deviations (z-scores) below the WHO reference median and/or a mid-upper arm circumference (MUAC) <11.5 cm and/or edema
- Moderate acute malnutrition (MAM): weight-for-height between -3.0 to <-2.0 z-scores below the WHO reference median and/or a MUAC from 11.5 cm to <12.5 cm.

The focus on children 6-59 months reflects the research showing the first years of life beginning at conception are the most critical for growth and development, and malnutrition treatment programs may have the greatest impact in children in these early years.[11, 12]

1.1.3 Overview of the Community-based management of acute malnutrition (CMAM)

In the past 20 years, great progress was made to refine the diagnostic tools, therapeutic food products and delivery model to reach more acutely malnourished children with treatment. The Community-based Management of Acute Malnutrition (CMAM) approach was adopted by the global nutrition sector after it was piloted in the early 2000's.[13-15] CMAM is comprised of four key components:

- community outreach and mobilization,
- inpatient treatment of SAM with medical complications,
- outpatient treatment of SAM without medical complications, and
- services or supplementary feeding for MAM.[16]

Prior to CMAM, treatment was delivered only on an inpatient basis using therapeutic milks (F75 and F100). Inpatient care presented many challenges including over-crowding, cross-infection, long duration of hospital stay, and the high opportunity costs to families of completing a full course of treatment.[16] CMAM enabled health systems to deliver malnutrition treatment on a primarily outpatient basis, using ready-to-use therapeutic foods (RUTF) provided to the caregiver to feed children at home. Only children with medical complications required treatment on an inpatient basis.[17] The system shifted from a primarily inpatient to a primarily outpatient care model, with greater potential to increase coverage of treatment. Media covered the development of ready-to-use food as a 'magic bullet' that with more investment could save millions more lives.[18]

1.1.4 Challenges scaling CMAM

Nearly twenty years after the first CMAM pilots,[19] coverage of treatment remains at 25% or lower.[20] National health services grapple with scaling up a CMAM model that is costly and complex, with different supply chains for therapeutic and supplementary foods and challenges integrating the model into health systems.[20] In many contexts where resources are limited, governments and

humanitarian actors may not be able to support the scale-up of a CMAM model for SAM and separate supplementary feeding programs for MAM.[21] New solutions are needed to reach children more efficiently and effectively and increase the global coverage of treatment.

Low coverage of treatment may be due to many factors, related primarily to access and availability. Accessing care may be difficult or impossible for families due to the high opportunity costs of seeking treatment, long distances to health facilities, and lack of knowledge of services, among other reasons.[22] Availability of care may be affected by factors external to the humanitarian aid system including lack of funding, low or non-functioning local health systems, disruptions to the supply chains of ready-to-use foods and staffing. But within the humanitarian aid system, several inefficiencies in the way care is set-up and delivered also affect the availability of treatment.

1.1.5 Global oversight of SAM and MAM programs

In the current system, SAM and MAM are managed separately, using different food products, and following different protocols, and often in different programs that may or may not be offered in the same physical location. In contrast to the systematized nature of SAM treatment, with clear global guidelines from the World Health Organization (WHO) and national adoption in most countries where acute malnutrition is high, the treatment of MAM changes according to context and varies in the type of supplementary food product given,[23, 24] or whether a supplement is given at all.[25] Three different UN agencies have oversight on the protocols, supply chain and management of SAM and MAM treatment:

- United Nations Children's Fund (UNICEF), based in New York, manages treatment of SAM and the supply chain of RUTF;
- World Food Programme (WFP), based in Rome, manages treatment of MAM and the supply chain of ready-to-use supplementary food (RUSF) or fortified blended flours;
- WHO, based in Geneva, issues the guidelines and protocols followed by international actors and national governments.

1.1.6 An inefficient system to manage acute malnutrition

The system set up to deliver care is fragmented and the components may not always connect. Often in emergencies or when resources are scarce, the treatment of SAM is prioritized and children with MAM may not be eligible for treatment until their condition deteriorates into SAM. Supplementary feeding programs may be established outside the health system as part of either blanket or targeted feeding initiatives. Children with MAM are often left out of the health systems approach to nutritional treatment, leading to frustrated families and health care practitioners who see children with nutritional needs who do not yet qualify for therapeutic feeding. Coverage surveys may not always account for MAM so there is little data on the coverage of MAM treatment services.[26] There is no globally-accepted protocol for the management of MAM, only guidance on the management of MAM in specific circumstances.[23-25] Without global consensus on managing MAM, the burden of SAM remains high despite treatment advances.

1.1.7 A new vision to unite and simplify SAM and MAM management

The humanitarian community is thus faced with a paradox when it comes to managing SAM and MAM: with a continuously high burden of SAM, there may not be enough RUTF or financial resources to treat all children with MAM. But if MAM is not adequately addressed, the burden of SAM may remain high. If we can simplify and optimize the care of SAM to maximize resources and get further upstream of the problem to adequately address MAM, this in turn may help prevent SAM. To do so requires a re-thinking of the way we see malnutrition, to reconnect SAM and MAM as a continuum condition rather than as two separate conditions to be addressed separately. The dividing line for the weight-for-height definition of acute malnutrition is statistical, with no physiological reason to classify a child differently on either side of the -3 z-score cut-off.

This more holistic but simplified view of acute malnutrition should not lose sight of the most vulnerable children. As part of this movement towards optimizing treatment, we must also address the way we identify and treat children most at risk of mortality and adverse outcomes. The goal is to achieve the right balance between meeting the needs of the highest risk subgroups of children, such as the youngest, those with concurrent wasting and stunting, and others at high risk of mortality,[27-29] with a programming approach that simplifies treatment, saves money, and extends care to more children.

1.2 Rationale for the ComPAS project

The Combined Protocol for Acute Malnutrition Study (ComPAS) was conceived to test hypotheses about how treatment could be combined and simplified to reach more children when resources are limited. The 'combined' aspect refers to treating SAM and MAM together in a single protocol. The 'simplified' aspect refers to the MUAC-based dosage protocol. ComPAS tested a protocol using only RUTF at doses designed to optimize growth and minimize cost at each stage of treatment, with admission, dosage and discharge determined by MUAC and oedema only. The vision for a simplified, combined protocol is to unite the treatment of uncomplicated SAM and MAM into a single protocol to improve coverage, quality, continuity of care and cost-effectiveness. A simplified, combined protocol for SAM and MAM that is non-inferior to standard treatment is primarily useful if it demonstrates improved cost-effectiveness and overall program efficiencies, conferring value for both the health system and patients and their families.

Hypothetically, a simplified and combined approach to treatment could eliminate the need for separate products, infrastructure and procedures for SAM and MAM, and enable treatment of MAM before children deteriorate into more costly and life-threatening SAM. By uniting the treatment of SAM and MAM and making MAM treatment more widely available, programs may eventually be able to reduce the caseload of SAM and reduce the costs associated with SAM treatment including the higher dosage of RUTF, systematic medications, treatment of complications and hospitalizations. Reducing the caseload of SAM may allow for a re-distribution of resources further upstream to address more of the MAM caseload, which could require a less intensive and less costly approach.

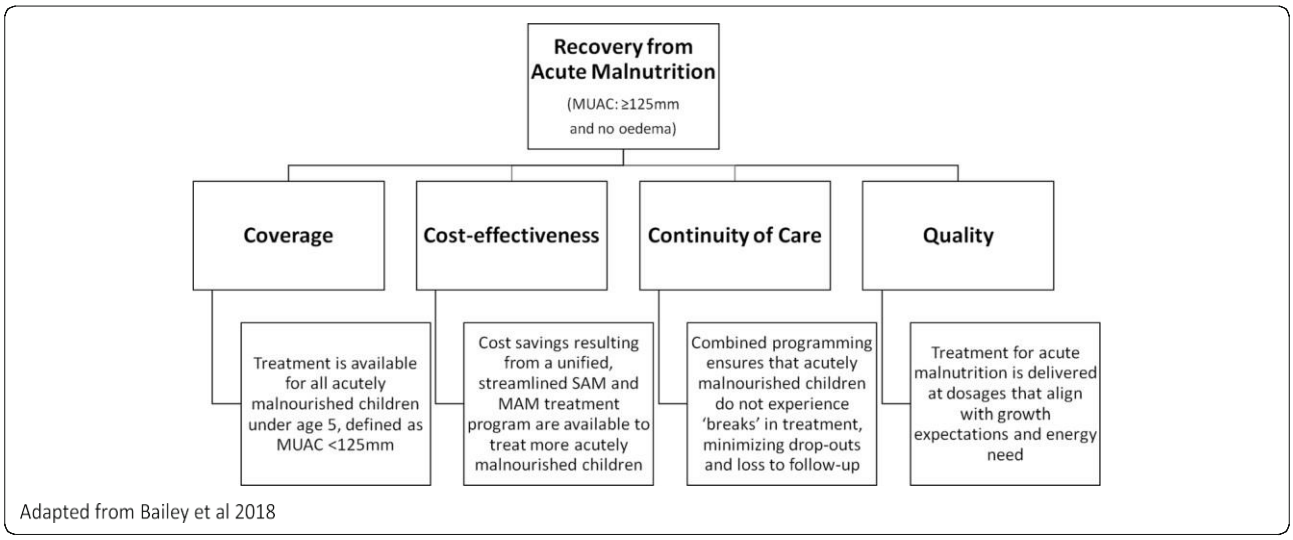

Figure 2: ComPAS theoretical framework

1.3 Thesis aim and objectives

The overall aim of this thesis was to generate evidence on a simplified, combined SAM and MAM approach to treat uncomplicated acute malnutrition in children 6-59 months, using a MUAC-based RUTF dosage protocol.

The thesis objectives were to:

1. Assess MUAC and weight gain trends in children recovering from acute malnutrition and estimate energy requirements correlated with MUAC category, to inform the development of a simplified, MUAC-based dosage protocol for SAM and MAM.

2. Evaluate if the simplified, combined protocol was non-inferior to the standard protocol in terms of recovery and assess whether it improved cost-effectiveness.

3. Explore the outcomes of subgroups of children with severely low weight-for-age and/or severely low MUAC, to contribute evidence on the optimal dosage required by children who may be at a high risk of near-term mortality.[27-30]

1.4 Description of PhD research

In the first stage of the research to address objective 1, routine program data from five countries was retrospectively analyzed to assess the rate of MUAC and weight gain as children recovered. The rate of MUAC and weight gain was correlated with estimated energy requirements according to MUAC category. We developed a MUAC-based RUTF dosage protocol that simplified and combined treatment for SAM and MAM children. **Paper II** of this thesis describes this first stage of the research and shares the science underpinning the development of the MUAC-based RUTF dosage protocol.

In the second stage of the research to address objective 2, the simplified, combined protocol was tested in a multi-country cluster-randomized controlled non-inferiority trial in Kenya and South Sudan. Our first hypothesis was that the combined protocol would be non-inferior to standard treatment because the protocol met the full energy needs of children with a MUAC <11.5 cm and provided a supplement to the diet of children with a MUAC between 11.5 cm and <12.5 cm. Aside from the dosage protocol, all other aspects of nutritional and medical management of children remained the same. Our second hypothesis was that the combined protocol would be more cost-effective, due to the streamlined approach and the optimization of dosage for children with SAM. **Paper I** describes the methods for the cluster-randomized controlled trial (RCT) and **Paper III** shares the results on the overall effectiveness and cost-effectiveness of a simplified, combined protocol.

In the final step of the research to address objective 3, the impact of the new dosage protocol on specific subgroups of children was explored, particularly those believed to be at a higher risk of adverse outcomes. Children that may fall into this category include those with concurrent wasting and stunting and/or low weight-for-age.[27, 28] Low weight-for-age has been shown to correlate well with concurrent wasting and stunting, as most children with a WHZ <-3.0 and a HAZ <-3.0 also have a WAZ <-3.0.[28, 29] The combination of low WAZ and low MUAC also identifies most children at risk of mortality.[28, 29] **Paper IV** explores the impact of the simplified dosage protocol on high-risk subgroups of children with a MUAC <11.5 cm and/or a WAZ <-3.0.

A follow-up study in the RCT assessed relapse and body composition four months post-discharge in Kenya. The aim of the follow-up study was to evaluate if children with MAM treated with RUTF as opposed to RUSF are at increased risk of adiposity, and if children with SAM treated with a reduced dosage of RUTF have an increased risk of relapse. The follow-up study goes beyond the scope of this thesis and the publication of results are shared in Annex J.

Table 1: Description of research undertaken for this thesis

Objective	**Addressed by Research paper**	**Specific objectives**	**Method for achieving objectives**
1	II	Compare MUAC and weight gain trends in children treated for acute malnutrition to assess if MUAC is a valid proxy of proportional weight gain during treatment. Calculate energy requirements needed to support observed weight and MUAC gain in children recovering from acute malnutrition and explore any differences by age and by MUAC category. Assess the ability of a simplified MUAC-based dosage protocol to meet the estimated energy needs of children recovering from acute malnutrition.	Secondary analysis of routine program data from Kenya, South Sudan, Chad, Pakistan and Yemen
2	I, III	Assess whether recovery in a simplified, combined protocol is non-inferior to standard treatment. Assess whether a simplified, combined protocol is more cost-effective than standard treatment.	Cluster-randomized controlled non-inferiority trial in Kenya and South Sudan
3	IV	Assess outcomes and response to treatment in children admitted with a MUAC <11.5 cm as two separate groups - those with a WAZ <-3.0 and those with a WAZ ≥-3.0 - both of which would be included in current *therapeutic* feeding programs, as well as children with a moderately low MUAC (i.e. MUAC between	Secondary analysis of ComPAS RCT data from Kenya and South Sudan

		11.5 cm and 12.5 cm) and a WAZ <- 3.0, who would be eligible for admission into *supplementary* feeding programs in many settings. Explore outcomes and response to treatment in each group by dosage protocol: a simplified, MUAC-based dosage in a combined treatment program compared to the weight-based dosage offered in standard care.	

1.5 PhD publications and related outputs

1.5.1 List of publications included in this thesis

Paper I: **Bailey J,** Lelijveld N, Marron B, Onyoo P, Ho LS, Manary M, Briend A, Opondo C, Kerac M. Combined Protocol for Acute Malnutrition (ComPAS) in rural South Sudan and urban Kenya: study protocol for a randomized controlled trial. Trials. 2018; 19(1):251. https://doi.org/10.1186/s13063-018-2643-2.

Paper II: Chase RP, Kerac M, Grant A, Manary M, Briend A, Opondo C, **Bailey J**. Acute malnutrition recovery energy requirements based on mid-upper arm circumference: Secondary analysis of feeding program data from 5 countries, Combined Protocol for Acute Malnutrition Study (ComPAS) Stage 1. PLoS One. 2020;15(6):e0230452. https://doi.org/10.1371/journal.pone.0230452.

Paper III: **Bailey J,** Opondo C, Lelijveld N, Marron B, Onyo P, Musyoki EN, Adongo SW, Manary M, Briend A, Kerac M. A simplified, combined protocol versus standard treatment for acute malnutrition in children 6-59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan. PLoS Med. 2020;17(7):e1003192. https://doi.org/ 10.1371/journal.pmed.1003192.

Paper IV: **Bailey J**, Lelijveld N. Khara T, Dolan C, Stobaugh H, Sadler K, Lino Lako R, Briend A, Opondo C, Kerac M, Myatt M. Response to Malnutrition Treatment in Low Weight-for-Age Children: Secondary Analyses of Children 6–59 Months in the ComPAS Cluster Randomized Controlled Trial. Nutrients. 2021; *13*, 1054. https://doi.org/10.3390/nu13041054.

1.5.2 ComPAS research publications included in the annex

Lelijveld N, Musyoki E, Adongo SW, Mayberry A, Wells JC, Opondo C, Kerac M, **Bailey J**. Relapse and post-discharge body composition of children treated for acute malnutrition using a simplified, combined protocol: A nested cohort from the ComPAS RCT. PLOS One. 2021; 16(2):e0245477. https://doi.org/10.1371/journal.pone.0245477.

Lelijveld N, **Bailey J**, Mayberry A, Trenouth L, N'Diaye DS, Haghparast-Bidgoli H, Puett C. The "ComPAS Trial" combined treatment model for acute malnutrition:

study protocol for the economic evaluation. Trials.2018; 19(1):252. https://doi.org/10.1186/s13063-018-2594-7 PMID: 29690899.

1.5.3 Related publications I authored or co-authored during my PhD

Bailey J, Chase RP, Kerac M, Briend A, Manary M, Opondo C, Gallagher M, Kim A. Combined protocol for SAM/MAM treatment: The ComPAS study. Field Exchange 53, November 2016. p44. www.ennonline.net/fex/53/thecompasstudy.

Briend A, Alvarez JL, Avril N, Bahwere P, **Bailey J,** Berkley JA, Binns, P, Blackwell N, Dale N; Deconinck H, Delchevalerie P, Dent N, Gallagher M, Guerrero S, Hanson K, Kerac M, Manary M, Mwangome MK, Myatt M, Phelan KPQ, Pietzsch S, Ubach NS, Shepherd S, van der Kam S, Vargas A, Whitney S. Low mid-upper arm circumference identifies children with a high risk of death who should be the priority target for treatment. BMC Nutrition. 2016;26(3).

Tesfai C and **Bailey J**. Breaking down the barriers to treating malnutrition. The New Humanitarian. 18 January 2017. https://www.thenewhumanitarian.org/opinion/2017/01/18/breaking-down-barriers-treating-malnutrition.

Marron B, Onyo P, Musyoki EN, Adongo SW, **Bailey J.** ComPAS trial in South Sudan and Kenya: Headline findings and experiences. Field Exchange issue 60, July 2019. p19. www.ennonline.net/fex/60/compastrialsouthsudankenya.

Kozuki N, Seni M, Sirat A, Abdullahi O, Adalbert MFE, Biotteau M, **Bailey J,** Goldsmith A, Dalglish S. Factors affecting decision-making on use of combined/simplified acute malnutrition protocols in Niger, north-east Nigeria, Somalia and South Sudan. Field Exchange issue 60, July 2019. p38. www.ennonline.net/fex/60/acutemalnutritionprotocols.

Bailey J. Tackling acute malnutrition. Medium. 27 July 2020. https://medium.com/airbel/tackling-acute-malnutrition-df96bbd79b7a.

Kerac M, McGrath M, Connell N, Kompala C, Moore WH, **Bailey J,** Bandsma R, Berkley JA, Briend A, Collins S, Girma T, Wells JC. 'Severe malnutrition': thinking deeply, communicating simply. BMJ Glob Health. 2020;5(11). doi:10.1136/ bmjgh-2020-003023.

Gluning I, Kerac M, **Bailey J,** Bander A, Opondo C. The management of Moderate Acute Malnutrition (MAM) in children aged 6-59 months: A systematic review and meta-analysis. medRxiv. 2021. https://doi.org/10.1101/2021.01.16.21249861.

1.5.4 Selected talks and presentations

CMAM 20 Years On: Going to Scale in Fragile Contexts. IRC experience implementing a simplified & combined treatment protocol. 23 March 2021.

Ministry of Health and nutrition partners in Ethiopia. Results from research on the simplified protocol in the ComPAS RCT and IRC routine programming. 5 February 2021.

Ministry of Health and the Emergency Nutrition Advisory Committee in Kenya. Final results from the ComPAS trial. 9 October 2020.

The Future of Food Assistance for Nutrition: Evidence Summit II. Continuum of Care, Wasting and Avoiding the MAM/SAM Dichotomy. 5 October 2020. https://evidencesummit2.wordpress.com/october-5th-2020-day-of-the-evidence-summit-agenda/.

Ministry of Health in South Sudan. Final results from the ComPAS trial. 8 July 2020.

Wasting-Stunting Technical Interest Group, Emergency Nutrition Network. ComPAS low weight-for-age analyses. 12 May 2020.

WHO, UNHCR, UNICEF and WFP Technical Consultation on Simplified Approaches for the Treatment of Wasting. Preliminary results from the ComPAS trial. 26 March 2019.

UNICEF and WFP Eastern and Southern Africa Regional Office. Preliminary results from the ComPAS trial. 7 March 2019.

World Food Programme: Global Nutrition Team Meeting. Preliminary results from the ComPAS trial. 6 December 2018.

Council of Research and Technical Advice on Acute Malnutrition (CORTASAM) and the No Wasted Lives Coalition: Annual Meeting. Preliminary results from the ComPAS trial. New York City, New York, United States. 13 November 2018.

FHI360 CMAM Consultation: Update to the 2008 CMAM Guidelines. Review of the evidence on MAM treatment and combined SAM/MAM programming. 14 March 2018.

Médecins Sans Frontières General Assembly. ComPAS Trial: Streamlined SAM + MAM protocol. New York City, New York, United States. 16 June 2016.

Global Nutrition Cluster. ComPAS stage 1 results and next steps. Washington D.C., United States. 31 March 2016.

Chapter 2: Review of the literature

2.1 Description of methods for the narrative review

At the time when I began my PhD work, most published research studies had looked only at SAM or MAM treated with separate protocols.[14] There was only one published study on the integrated treatment of SAM and MAM in a single protocol which used a weight-based dosage protocol.[31]

This section presents a narrative review of the literature conducted on PubMed/Medline in November 2016 at the start of my PhD, and then updated in April 2019 and March 2021. This is a summary of key evidence related to ComPAS through March 2021, excluding the evidence produced from the ComPAS research itself. A full systematic review was not conducted because I am aware of only two other published studies that have tested a combined SAM and MAM protocol,[31, 32] even as new studies are on-going.[33-35] This narrative review searched for evidence on the novel aspects of the protocol tested in ComPAS, with a brief overview of the key research for each topic:

(1) the combined treatment of SAM and MAM in a single protocol,
(2) mid-upper arm circumference as the primary anthropometric criteria guiding admission, monitoring and discharge in nutritional treatment,
(3) energy requirements related to rate of growth during recovery from acute malnutrition, and
(4) the use of RUTF for MAM.

Only papers related to acute malnutrition in children 6-59 months were included. Terms related to "acute malnutrition," "wasting," "integrated treatment," "mid-upper arm circumference," "ready-to-use food," and "energy needs," were used to identify key papers without a time limit. The search strategy is available in Annex A. A review of references from key papers and grey literature sources including the Emergency Nutrition Network and State of Acute Malnutrition websites were also searched. The evidence is organized by topic area below.

2.2 Combined treatment of SAM and MAM in a single protocol

There were two studies that met the criteria for combined SAM and MAM treatment in a single protocol: one prior to ComPAS in Sierra Leone in 2013-2014[31] and one that originated after ComPAS began in Burkina Faso in 2017-2018.[32] The cluster-randomized controlled trial in Sierra Leone

included 1,100 children in the integrated protocol arm and 857 children in the standard treatment arm. It found improved recovery, increased program coverage and lower therapeutic food costs in the integrated protocol compared to standard care.[31] In the intervention arm, children received different doses of RUTF according to MUAC category: <11.5 cm received 175 kcal/kg/day, and 11.5 to <12.5 cm received 75 kcal/kg/day. Children in the intervention were also discharged with a package of preventive health care and infant and young child feeding (IYCF) support. In the standard care arm, children received 200 kcal/kg/day of RUTF for SAM and super cereal plus for MAM (1,250 kcal/day). The study found similar recovery (83% (95% CI 81 to 85) vs. 79% (95% CI 77 to 82)) and higher coverage (71% vs. 55%, *p*=0.0005) in the intervention arm, as well as a reduced caseload of SAM due to earlier treatment of children presenting with MAM. Children receiving the integrated protocol also recovered more rapidly, with greater MUAC gain and a higher WHZ at discharge. The cost of RUTF to treat a SAM case was less in the integrated program: $36 vs. $68 in the standard program.

A single-arm proof of concept trial in Yako district, Burkina Faso evaluated an integrated treatment protocol for SAM and MAM using a combination of weight and MUAC-based criteria to determine dosage (the OPTIMA study).[32] The OPTIMA protocol used a graduated dosing protocol with three key categorizations used to determine treatment protocol: MUAC <11.5 and/or oedema received 175 kcal/kg/day, MUAC 11.5 to <12.0 cm received 125 kcal/kg/day, and MUAC 12.0- <12.5 cm received 75 kcal/kg/day. Mothers in the OPTIMA trial were trained to screen and refer their own children using MUAC and oedema. The study aimed to demonstrate that this approach adhered to SPHERE standards of recovery rates of ≥75%. It included 4,958 children treated with the integrated protocol. Overall recovery of trial participants was 86.3% (95% CI 85.4, 87.2) and for the 16% of children admitted with MUAC <11.5 cm and/or oedema, recovery was 70.5% (95% CI 67.5, 73.5). The average RUTF consumption for children who met the standard SAM admission criteria was 72.2 sachets/child, nearly half the sachets planned by UNICEF in Burkina Faso to treat a child with SAM (140 sachets on average). Children who met the criteria for MAM also consumed less ready-to-use food, averaging 54.3 sachets/child in the study compared to 60-90 sachets of RUSF planned for children in a supplementary feeding program.

2.3 MUAC-only based nutrition programming

2.3.1 MUAC to identify children at high-risk of mortality

MUAC is currently one of two primary anthropometric criteria used for admission and discharge in CMAM programs, along with WHZ.[36, 37] MUAC and WHZ identify similar but not completely overlapping subsets of children, particularly in certain contexts.[38] WHZ may overestimate the prevalence of wasting in pastoralist populations with longer, leaner body types.[39]

Multiple studies show that mid-upper arm circumference is effective for identifying children at highest risk of mortality,[40-50] but debate continues over whether MUAC alone detects all children at risk of mortality.[48, 51-54] MUAC tends to identify children who are younger and shorter[48, 55] but these children also have a higher mortality risk.[40, 50, 56] Higher sensitivity for the same level of specificity may be achieved by raising the MUAC cut-off.[45] In a study of children receiving therapeutic feeding in South Sudan, all deaths were identified when the MUAC cut-off was increased to 13.0 cm.[46] In Bangladesh, age-stratified MUAC cut-offs have been proposed ranging from <12.0 cm for WHZ <-3.0 and <12.5 cm for WHZ <-2 for ages 6-24 months, up to <13.5 cm for WHZ <-3.0 and <14.0 cm for WHZ <-2 for ages 37-60 months.[57]

2.3.2 Adding WAZ to MUAC to detect children at high-risk of mortality

A combination of MUAC and weight-for-age z-score (WAZ) has been studied for its ability to detect near-term deaths in children with concurrent wasting and stunting and/or low WHZ.[28, 29] Children with concurrent wasting and stunting (defined as WHZ <-2 and HAZ <-2) are among the most vulnerable to mortality of all malnourished children,[28-30] but there is no set of admission criteria specifically targeted to identify them for therapeutic feeding.[17] Adding WAZ to MUAC as a criterion for therapeutic feeding admissions may address concerns that MUAC-only programming excludes children who meet WHZ criteria but not MUAC criteria.[58] Low WAZ captures children at high risk of mortality who would have been identified by WHZ but not MUAC, while focusing the targeting of programs on the most vulnerable children with multiple anthropometric deficits.[28, 29] A WAZ <-3.0 was identified as a risk factor for deterioration among children diagnosed with MAM in Sierra Leone.[59]

2.3.3 MUAC as a discharge criterion for treatment

Discharging children who meet a MUAC of 12.5 cm with no oedema for two consecutive visits is associated with low mortality,[60, 61] low relapse,[61-63] high recovery and good weight gain,[55, 64, 65] good MUAC gain[66] and longer lengths of stay for the most severely malnourished.[61, 64] Discharging a child before their MUAC reaches 12.5 cm is associated with a higher risk of relapse.[62]

2.3.4 MUAC to monitor progress during treatment

In addition to admission and discharge, some studies have assessed the ability of MUAC to monitor progress during treatment.[67] MUAC gain tends to mirror weight gain during treatment[53, 67-69] and MUAC and weight gain are affected similarly by acute illness.[67]

2.3.5 MUAC as a simplified tool for detection and treatment

MUAC-only programming is simpler and may be easier to implement than programs that also use WHZ.[45, 70, 71] Recent studies have shown that mothers are able to use MUAC to screen their own children for wasting.[72, 73]

2.4 Rate of growth and energy requirements during recovery from SAM or MAM

2.4.1 Energy requirements during recovery from acute malnutrition

Maintenance energy requirements for a child recuperating from acute malnutrition has been estimated at approximately 82 kcal/kg/day.[74, 75] The energy cost of growth is uncertain but estimated as between 1.66 kcal/g^{-1} [76] to 4.4 kcal/g^{-1},[74] which is often rounded to 5 kcal/g for practical purposes.[77]

2.4.2 Energy provision in nutritional treatment programs

In an inpatient setting, severely wasted children have been shown to gain from 10-15g/kg/day,[78, 79] to 20 g/kg/day.[80] Energy provision of 150-220 kcal/kg/day is recommended for the inpatient treatment of SAM.[78, 81] In an outpatient setting, typical weight gain is closer to 4.5-6.8g/kg/day[82] or 5.5g/kg/day,[83] but national protocols typically provide 175-200 kcal/day for the outpatient treatment of SAM, an amount determined from studies of weight gain in the inpatient setting.[84, 85]

2.4.3 Reducing the dosage of therapeutic food

Recent work has hypothesized that the therapeutic food dosage could thus be reduced in outpatient programs without a negative impact on growth or recovery.[31, 32, 86, 87] Several studies have assessed the impact of reduced or alternate dosage protocols on recovery from SAM or MAM.[31, 32, 83, 86, 87] An observational study in Myanmar reduced the dosage of RUTF to one sachet (500 kcal) per day after children reached a WHZ ≥-3 or MUAC ≥11.0 cm, and achieved 90.2% recovery, 2.0% defaulted, 0.9% were classified as non-responders with no deaths reported.[86] A randomized controlled trial in Burkina Faso reduced the dosage of ready-to-use therapeutic food as children with severe malnutrition gained weight and found that overall recovery rates remained above global Sphere standards. For children with uncomplicated SAM (WHZ <-3.0 and/or MUAC <11.5 cm) reducing the RUTF dose by 30-53% after two weeks' of standard treatment did not reduce overall weight or MUAC gain velocity or affect recovery or lengthen treatment time. There was a small but significant negative effect on linear growth, especially among children under 12 months.[87] As described above in the section on integrated treatment of SAM and MAM, an operational study in Burkina Faso provided 175 kcal/kg/day for children with a MUAC <11.5 cm, 125 kcal/kg/day for children with a MUAC 11.5to <12.0 cm, and 75 kcal/kg/day for children with a MUAC 12.0 to <12.5 cm. Overall recovery across all three groups was 86.3% (95% CI 85.4, to 87.2), with 70.5% (95% CI 67.5 to 73.5) recovering among those admitted with a MUAC <11.5 cm and/or oedema.[32] An integrated SAM/MAM trial in Sierra Leone provided 175 kcal/kg/day for children with a MUAC <11.5 cm and 75 kcal/kg/day for children with a MUAC between 11.5 to <12.5 cm, and reported recovery of 83% (95% CI 81 to 85) in the intervention arm compared to 79% (95% CI 77 to 82) in the standard dosage arm.[31]

2.4.4 Rate of weight and MUAC gain during treatment

Rate of weight and MUAC gain is most rapid during the earliest stages of treatment, and as children begin to recover from acute malnutrition, their rate of weight and MUAC gain slows.[68, 69, 84, 88] Average weight gain also tends to mirror average MUAC gain.[53, 67-69, 88] Thus, response to treatment and supplemental energy needs decrease as children approximate normal growth[80]and gain in weight and MUAC,[83, 88] giving rise to the practice to reduce the dosage as children transition from SAM into MAM treatment. Supplementary feeding programs for treatment of MAM in children 6-59 months typically provide a supplement to the family diet, rather than meeting total energy needs.[23, 24] A study analyzing the theoretical performance of different dosage protocols applied against a population of children under treatment in Niger found that energy provision may be reduced in the latter weeks of treatment.[83]

2.5 Use of RUTF for treatment of MAM

2.5.1 Strategies to manage MAM

There is currently no formal WHO protocol for the treatment of MAM, only programmatic guidance,[23-25] and expert guidance on how to meet the nutrient needs of moderately malnourished children.[89, 90] Multiple strategies have been recommended for the management of MAM, including food supplementation, micronutrient supplementation and/or counseling.[24, 25, 91] Children with MAM have an elevated risk of mortality, morbidity and deterioration into SAM.[14, 92-94] Systematic reviews published in 2019 and 2021 found that children with MAM are more likely to recover with food supplementation as opposed to counseling, with or without micronutrient supplementation alone.[91, 95] Counseling alone may not be sufficient particularly in areas of food insecurity.[59, 96, 97]

2.5.2 Lipid-based nutrients supplements vs. fortified blended flours

Many of the studies evaluating MAM treatment with food supplements have assessed the effectiveness of lipid-based nutrient supplements compared to fortified blended flours. Studies have shown the provision of a lipid-based nutrient supplement (LNS), like ready-to-use food, results in improved recovery compared to fortified blended flours.[14, 95, 97-107] The composition of fortified

blended flours used for young children was improved to include dairy proteins and reduce anti-nutrients,[108-110] and improved products such as corn-soya blend (CSB) ++ have been shown to be comparable to LNS in some studies.[99, 111-113] The Treat Food study in Burkina Faso evaluated the effectiveness of matrix (CSB vs. LNS), soy quality and milk content and found better recovery and higher proportional accretion of fat-free mass among children who received LNS.[76] Fat-free mass is a component of lean mass, which is associated with improved immunity, survival and development.[76] LNS was also found to improve hemoglobin and iron status better than CSB.[100, 114]

2.5.3 Protein composition in lipid-based nutrient supplements

Among the different types of lipid-based nutrient supplements used for treatment of MAM, those with the highest quality of protein, such as dairy protein, may be the most effective.[23, 76, 101, 115-118] RUTF was designed for the treatment of SAM and was originally based on the composition of F100 therapeutic milk, which is dairy-based.[78] RUSF was designed for the treatment of MAM[23] and originally did not contain dairy protein,[108] though in recent years milk-based proteins have been added.[116, 119] In Malawi, moderately malnourished children given soy + whey RUSF were more likely to remain well-nourished (67%) than those treated with corn soy blend (CSB)++ (62%) or soy RUSF (59%) (p = 0.01).[101] Higher recovery has also been shown in children given a whey RUSF (83.9%) compared to soy RUSF (80.5%) (risk difference 3.4, 95% CI 0.3 to 6.6, p <0.04), with a higher mean MUAC at discharge (p <0.009), greater MUAC gain during treatment (p <0.003), higher mean WHZ at discharge (p <0.008), and greater weight gain (p <0.05).[116] Lower recovery and lower weight gains were seen in children with SAM treated with a 10% milk RUTF compared to 25% milk RUTF.[120] A random effects meta-analysis of three trials comparing whey/milk LNS vs. no animal product/soy LNS found no evidence of a difference in recovery, risk of progression to SAM or risk of death.[95] In recent years, new versions of RUF have been tested with alternate compositions.[76, 115, 121-128] In one study, a milk-free amino acid-enriched soya-maize-sorghum (SMS) RUTF was shown to be non-inferior to milk-based RUTF in terms of recovery and length of stay in children with SAM, with a superior ability to restore body iron stores.[115, 122]

2.5.4 RUTF for the treatment of MAM

RUTF has occasionally been used in the treatment of MAM in programmatic settings[129] and tested in research settings with good recovery and response to treatment.[13, 31, 32, 97, 102, 130] The physiology of children with SAM and MAM is similar and therefore the treatment of MAM using RUTF is expected to be similar to the treatment of SAM using RUTF.[131] A systematic review of LNS used for MAM treatment indicated increased recovery with RUTF compared to RUSF in sub-analyses.[97]

2.6 Implications of available evidence

In summary, the evidence available before ComPAS – and the evidence which has accrued from other studies over its duration – suggested that a MUAC-based protocol may be simpler to use and could better identify children at high risk of mortality, especially when combined with WAZ as admission criteria to therapeutic feeding programs.[28, 29, 48] Furthermore, a tapered dose of RUTF as children reach the end of treatment appears to theoretically meet children's energy requirements[83] and leads to similar recovery and program outcomes,[31, 32, 86, 87] and LNS could improve recovery and fat free mass accretion in children recovering from MAM.[76] Finally, integrated treatment of SAM and MAM improves cost-effectiveness while maintaining program effectiveness.[31, 32]

These findings are consistent with the foundational hypotheses of this PhD research, that a simplified, combined protocol for acute malnutrition using a MUAC-based RUTF dosage protocol would be as effective as standard treatment but more cost-effective.

2.7 Building the evidence on a simplified and combined protocol

This PhD research aimed to build on the only other combined protocol study published as of 2016,[31] as well as test several innovative components of a simplified, combined treatment protocol. ComPAS was the first randomized controlled trial I am aware of to test a MUAC-based dosage protocol for the treatment of acute malnutrition. It added to the Maust et al. 2015[31] study and the existing body of evidence by:

(1) basing dosage on MUAC instead of weight,
(2) comparing a combined protocol with a control group using ready-to-use supplementary food for MAM, instead of fortified blended flours,
(3) comparing against a control group with an equivalent definition of recovery (MUAC ≥12.5 cm and no oedema, instead of WHZ ≥-2),
(4) using a larger sample size across two countries, with both urban and rural contexts,
(5) analyzing overall program cost-effectiveness from the household, health facility and program perspectives, and
(6) exploring outcomes and response to treatment in children with a severely low weight-for-age, who may be at a higher risk of mortality or adverse outcomes.

Chapter 3: Methods

3.1 Overview of the PhD research process

3.1.1 Pre-PhD: finding funding and building the research coalition

After sharing the initial idea for a simplified, combined protocol at a meeting of nutrition advisors in January 2014 (described in the Preface), I wrote a concept note for the research. I reached out to academics I considered mentors- including Dr. André Briend and Dr. Mark Manary- and asked them to review the concept paper. I learned that Dr. Manary had led an integrated SAM/MAM study in Sierra Leone that we could build on.[31] Dr. Manary's team had used two different products and continued to base dosage on weight, so there were some differences from the ideas we sought to test in a simplified, combined protocol.

In April 2014 I presented the idea to a group of nutrition colleagues again, in more detail. As a result of this presentation, the Office of U.S. Foreign Disaster Assistance (OFDA) invited me to submit a funding proposal on behalf of the International Rescue Committee (IRC). I reached out to my colleagues at Action Against Hunger (AAH) to develop a research partnership, and I spent the next few months developing the funding proposal, engaging partners, and laying the groundwork for what would soon become the ComPAS research coalition. Through a sub-grant via the No Wasted Lives Coalition, we received additional funding from the Children's Investment Fund Foundation (CIFF) to complement our funding from OFDA.

I met with my future PhD supervisor, Dr. Marko Kerac, in May 2014 at the International Symposium on Understanding Moderate Malnutrition in Children for Effective Interventions in Vienna, Austria. I hoped to develop the research into a PhD and asked Dr. Kerac if he might be interested in supervising. I was aware there was much I did not know-- as a public health professional with a background in humanitarian response- and I sought to develop the necessary research skills through a PhD. Dr. Kerac introduced me to my second supervisor, Dr. Charles Opondo, a medical statistician and clinical trialist.

I reached out to a scientific committee of experts in pediatrics, nutrition, epidemiology, and statistics to guide the study and review progress at key milestones. In addition to my supervisors Dr. Kerac and Dr. Opondo, the initial scientific committee also included Dr. André Briend, Dr. Mark Manary and Dr. Rachel Chase.

I was also aware that a study that challenges the status quo would potentially come up against political and economic resistance, and so I invited a group of representatives from UNICEF, WFP, WHO, United Nations High Commissioner for Refugees (UNHCR), European Civil Protection and Humanitarian Aid Operations (ECHO), and OFDA to participate in a policy stakeholder committee. I sought to develop a research plan that could directly inform future policy and practice. I met with senior nutrition advisors from UNICEF, WFP and WHO to discuss the ideas behind a simplified and combined protocol and the UN's perspectives on the continuum of care between SAM and MAM.

We continued to expand the research over the subsequent years and built a coalition of nutrition experts, humanitarian programmers, epidemiologists, scientists and statisticians across the IRC, AAH, LSHTM, Médecins Sans Frontières (MSF), No Wasted Lives, the Wasting Stunting Technical Interest Group, UNICEF, WFP, and the Ministries of Health in Kenya and South Sudan.

3.1.2 Research process during the PhD

After I registered as a PhD candidate in January 2016, I convened a meeting of the scientific committee and the IRC, AAH and LSHTM research partners to:

(1) Review the research on energy requirements and rate of growth in children recuperating from acute malnutrition to propose a simplified, MUAC-based dosage protocol, and
(2) Discuss potential study designs for the clinical trial.

In the first year of my PhD in 2016, I worked closely with the scientific committee to finalize the analyses of rate of MUAC and weight gain and energy requirements to inform the MUAC-based dosage protocol. I developed the trial study protocol and analysis plan and sought feedback from the scientific committee to refine the study design. I hired the project coordinators and key staff to lead the research in each country. I submitted the study protocol for LSHTM ethical approval and supervised the submission of the protocol to the relevant national ethical committees in Kenya and South Sudan. At the end of 2016, I completed the narrative review of evidence and submitted my upgrading report to LSHTM.

In the second and third years of my PhD in 2017-2018, I hired and trained additional field-based staff, coordinated the development and piloting of digital and paper-based data collection tools, began recruitment in Kenya and South Sudan, visited the field sites in Kenya, and performed all trial management duties as the principal investigator. We completed treatment of the last enrolled child

in August 2018. I began cleaning and analyzing the data in September 2018 and prepared preliminary results to share with the research coalition partners and key stakeholders by the end of 2018.

In the fourth and fifth years of my PhD in 2019-2020, I finalized the analyses, prepared results for peer-reviewed publications, and presented the final results to relevant stakeholders including the Ministries of Health in South Sudan and Kenya, UNICEF, WFP and WHO.

The specific methods towards achieving each objective during the PhD research process are summarized below, with a full description of methods in the respective papers.

3.2 Summary of methods for objective 1

The first stage of research was a secondary analysis of routine patient card data from 5,518 children 6-59 months in SAM and MAM outpatient treatment programs in Kenya, Chad, South Sudan, Yemen and Pakistan. Data from the patient cards in Kenya, Chad, Yemen and Pakistan was entered into Excel files and cross-checked with double data entry by data entry clerks in the field offices of the NGO's in each country. An excel dataset was provided for the data from MSF-France in South Sudan, following the signing of a data sharing agreement. Ethical approval for this work was given from the LSHTM (reference 11820). Anonymized data from the five countries was received by the PI and stored on a password-protected IRC institutional server. The data were cleaned and merged into a single anonymized dataset by a statistician in preparation for analysis.

Analyses were reviewed by the ComPAS research team and scientific committee. The MUAC-based dosage protocol was developed in consultation with the scientific committee and approved for development into the simplified, combined protocol to be tested in the RCT.

A detailed description of the methods for this analysis can be found in **Paper II.**

3.3 Summary of methods for objective 2

The second stage of research was a cluster-randomized controlled non-inferiority trial that enrolled 4,110 children 6-59 months with SAM or MAM in Kenya and South Sudan. This stage was designed as a multi-country trial to increase generalizability across settings. Aweil East in South Sudan was

chosen because of AAH's long-term presence operating nutrition programs and because it represented a rural, humanitarian setting with a high burden of acute malnutrition. Nairobi, Kenya was selected as the second setting because of IRC's presence in the country and ability to work closely together with the MoH to implement the research to a high standard, as well as the high absolute numbers of acutely malnourished children in the urban slums. A cluster-randomized controlled design was chosen to improve simplicity of delivery and thus adherence to the protocol in each clinic and to improve the collection of cost data by protocol type. We tested for non-inferiority in the primary outcome of recovery because we did not anticipate that simplifying and combining treatment would improve recovery compared to standard treatment, rather we wanted to assess that recovery was at least as good as standard treatment. Ethical approvals were given by LSHTM (reference 11826), the Kenya Medical Research Institute (reference non-KEMRI 551) and the Ministry of Health in South Sudan (approved 21 November 2016). Enrollment for the trial began in May 2017 in both countries. Recruitment was completed in both countries by March 31, 2018, and the last children completed their treatment in July 2018 in Kenya and August 2018 in South Sudan.

A detailed description of the RCT methods can be found **Papers I and III.** The ethical approvals, consent form and data collection tools can be found in Annexes B-D.

To evaluate cost-effectiveness, an economic analysis was embedded within the RCT to account for program and household costs, inclusive of accounting records, key informant interviews with health care workers, and discharge exit interviews and focus group discussions with caretakers. The methods paper for the cost-effectiveness analysis can be found in Annex H.

3.4 Paper I: Methods for the cluster-randomized controlled trial

Paper I: **Bailey J,** Lelijveld N, Marron B, Onyoo P, Ho LS, Manary M, Briend A, Opondo C, Kerac M. Combined Protocol for Acute Malnutrition (ComPAS) in rural South Sudan and urban Kenya: study protocol for a randomized controlled trial. Trials. 2018; 19(1):251. https://doi.org/10.1186/s13063-018-2643-2.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	173611	**Title**	Ms.
First Name(s)	Jeanette		
Surname/Family Name	Bailey		
Thesis Title	Simplified, combined protocol for acute malnutrition in children 6-59 months: the ComPAS randomized controlled trial		
Primary Supervisor	Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMC Trials: Bailey J, Lelijveld N, Marron B, Onyoo P, Ho LS, Manary M, Briend A, Opondo C, Kerac M. Combined Protocol for Acute Malnutrition (ComPAS) in rural South Sudan and urban Kenya: study protocol for a randomized controlled trial. Trials. 2018; 19(1):251. https://doi.org/10.1186/s13063-018-2643-2.		
When was the work published?	April 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This is the publication of the study protocol for the ComPAS randomized controlled trial. I conceived the idea for the trial, and along with my co-authors MK, CO, AB, MM and BM, designed the study. I wrote the first draft of the manuscript, managed the revisions and feedback from co-authors, submitted the paper for peer-review, managed the peer-review responses and revisions, and finalized the paper for publication, with approval of all co-authors.

SECTION E

Student Signature	Jeanette Bailey
Date	1 April 2021

Supervisor Signature	Dr Marko Kerac
Date	15th April 2021

Bailey *et al. Trials* (2018) 19:251
https://doi.org/10.1186/s13063-018-2643-2

Trials

STUDY PROTOCOL Open Access

Combined Protocol for Acute Malnutrition Study (ComPAS) in rural South Sudan and urban Kenya: study protocol for a randomized controlled trial

Jeanette Bailey[1,2*], Natasha Lelijveld[2,3], Bethany Marron[1], Pamela Onyoo[4], Lara S. Ho[1], Mark Manary[5], André Briend[6,7], Charles Opondo[2] and Marko Kerac[2]

Abstract

Background: Acute malnutrition is a continuum condition, but severe and moderate forms are treated separately, with different protocols and therapeutic products, managed by separate United Nations agencies. The Combined Protocol for Acute Malnutrition Study (ComPAS) aims to simplify and unify the treatment of uncomplicated severe and moderate acute malnutrition (SAM and MAM) for children 6–59 months into one protocol in order to improve the global coverage, quality, continuity of care and cost-effectiveness of acute malnutrition treatment in resource-constrained settings.

Methods/design: This study is a multi-site, cluster randomized non-inferiority trial with 12 clusters in Kenya and 12 clusters in South Sudan. Participants are 3600 children aged 6–59 months with uncomplicated acute malnutrition. This study will evaluate the impact of a simplified and combined protocol for the treatment of SAM and MAM compared to the standard protocol, which is the national treatment protocol in each country. We will assess recovery rate as a primary outcome and coverage, defaulting, death, length of stay, average weekly weight gain and average weekly mid-upper arm circumference (MUAC) gain as secondary outcomes. Recovery rate is defined across both treatment arms as MUAC ≥125 mm and no oedema for two consecutive visits. Per-protocol and intention-to-treat analyses will be conducted.

Discussion: If the combined protocol is shown to be non-inferior to the standard protocol, updating guidelines to use the combined protocol would eliminate the need for separate products, resources and procedures for MAM treatment. This would likely be more cost-effective, increase availability of services, enable earlier case finding and treatment before deterioration of MAM into SAM, promote better continuity of care and improve community perceptions of the programme.

Trial registration: ISRCTN, ISRCTN30393230. Registered on 16 March 2017.

Keywords: Non-inferiority, Acute malnutrition, Cluster randomized trial, Community-based management of acute malnutrition, Mid-upper arm circumference, Ready-to-use therapeutic food, Kenya, South Sudan

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Background

Acute malnutrition is a major global public health problem affecting an estimated 52 million children under 5 years of age [1]. Of these, some 35 million have moderate acute malnutrition (MAM) and 17 million have severe acute malnutrition (SAM). The true burden of disease is however likely much higher. This is because most current estimates are based on cross-sectional survey data giving prevalence figures, whereas SAM and MAM, being short-lasting conditions, should ideally be assessed in terms of incidence [2, 3]. Malnutrition in all its forms is an underlying cause of 3.1 million (45%) of deaths among children under 5, with wasting alone responsible for 875,000 child deaths per year [4].

Despite the availability of effective, evidence-based treatment programmes, especially for SAM, their public impact is often limited by low coverage of the affected population. According to recent estimates, less than 20% of children with SAM receive the treatment they need [5]. Figures for MAM programme coverage are unknown—but are likely to be lower since it is often perceived to be less of a priority compared to SAM. This is despite wasting, the major manifestation of both SAM and MAM, being on a continuum, with the cut-off between the two defined statistically (based on weight-for-height/length standard deviations from the median) rather than by any distinguishable clinical changes.

In humanitarian settings (as well as many other non-emergency but fragile contexts where malnutrition is common), current international and national recommendations involve treating SAM and MAM in separate programmes, using separate protocols and separate products managed by two large but separate United Nations agencies. SAM is treated with ready-to-use therapeutic food (RUTF) in an outpatient therapeutic programme (OTP), with oversight and technical guidance from the United Nations International Children's Fund (UNICEF). MAM is treated with ready-to-use supplementary food (RUSF) or fortified corn soy blend ++ (CSB++) in a supplementary feeding programme (SFP), with oversight and technical guidance from the World Food Programme (WFP). The shortcomings of this system include the following: (1) it is logistically complicated to implement, requiring the procurement of two different nutritional products and the set-up of two separate programs, in coordination with two separate UN agencies, (2) it is consequently expensive, and (3) it often results in the prioritization of SAM over MAM: many aid agencies and governments offer treatment only of SAM due to the challenges associated with procuring two products and coordinating two programmes. This results in a situation where treatment may not be available to children with MAM until they deteriorate to SAM.

Responding to these current challenges, the Combined Protocol for Acute Malnutrition Study (ComPAS) will assess the effectiveness of a simplified, combined protocol for the treatment of uncomplicated SAM and MAM for children 6–59 months. The study aims to improve the quality, coverage, continuity and cost-effectiveness of care (Fig. 1). The combined protocol uses one product (RUTF) for both SAM and MAM, at doses designed to optimize growth and minimize cost at each stage of treatment. Admission and discharge is assessed using only mid-upper arm circumference (MUAC) and oedema [6]. Differences between the combined and standard protocol are presented in Table 1.

ComPAS was inspired by increasing realization that combining the treatment of SAM and MAM makes biological sense—since wasting is a continuum condition rather than two distinct and different problems; operational and financial sense—since staff skill set and infrastructure are very similar for the two programmes and may thus usefully be shared; and public health sense—since a combined programme should be easier to access and should thus improve overall programme coverage.

Early data supporting the hypothesis of clinical non-inferiority comes from a 2013 Washington University trial in Sierra Leone [7]. This study explored the efficacy of an integrated SAM/MAM treatment protocol using one product (RUTF) but at different doses for children <115 mm (175 kcal/kg/day) and 115 to <125 mm (75 kcal/kg/day). Controls followed standard care guidelines: RUTF for SAM and SFP with CSB++ for MAM. Results showed that the integrated programme had a reduced caseload of SAM, due to earlier treatment of children presenting as MAM, with a similar recovery rate (83% vs. 79%) and higher coverage (71% vs. 55%, $p = 0.0005$). Children who received integrated management recovered more rapidly, with greater MUAC gain and higher weight-for-height Z-score (WHZ) upon discharge.

Other data supporting the use of a single nutritional product but at different doses comes from our own secondary analysis of routine nutrition programme data from five countries (Yemen, Pakistan, South Sudan, Chad, Kenya) and three different agencies (International Rescue Committee (IRC), Action Against Hunger—USA (ACF-USA), and Médecins Sans Frontières—France (MSF-France)) [8]. This analysis used observational data to assess the rate of growth of children recovering from acute malnutrition in OTPs and SFPs in order to determine energy requirements and propose an optimized dose of RUTF that correlates with the MUAC category. We found that:

- Growth trends in MUAC mirror those of proportional weight gain and rates of MUAC and weight gain slow with increasing MUAC.
- As the rates of MUAC and weight gain slow, proportional energy needs decrease.
- Total energy needs of 95% of all children with a MUAC <125 mm can be met with 1000 kcal/day.

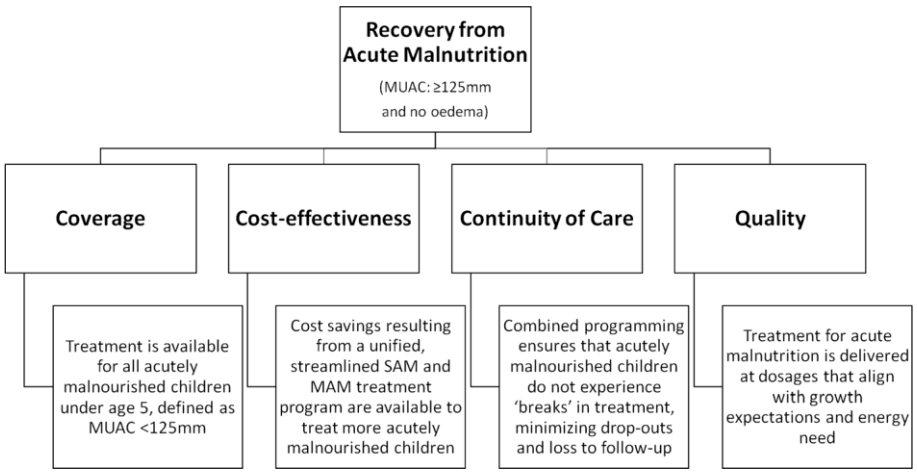

Fig. 1 ComPAS conceptual framework

Based on these observations, the combined and simplified MUAC-based dosage protocol was developed, and it is this which is being tested in the current study:

- Children with a MUAC <115 mm and/or oedema receive two sachets of RUTF per day (1000 kcal).
- Children with a MUAC 115 to <125 mm receive one sachet of RUTF per day (500 kcal).

The objective of our current project is to assess the effectiveness of a combined SAM/MAM protocol compared to standard care (separate SAM/MAM treatment) in two countries: Kenya and South Sudan. The outcomes of stage 2 are described in Table 2.

We will add to the available evidence by (1) testing a dosing protocol based on the MUAC category, not weight [6, 9, 10]; (2) comparing against a control SFP using RUSF, instead of CSB++; (3) comparing equivalent definitions of recovery in both control and intervention groups; (4) using a larger sample size across two countries; and (5) conducting a thorough cost-effectiveness analysis using proven methodologies.

The publication of this study protocol aims to improve transparency and share information to support the development of similar studies that seek to simplify the protocols for acute malnutrition and increase the availability of treatment.

Methods/design

Trial design

The study is a multi-country cluster randomized controlled non-inferiority trial. The units of randomization are health facilities stratified by country and then randomly assigned to the control or intervention group. Children in the control group receive the standard protocol while those in the intervention group receive the combined protocol. The study includes a total of 24 clusters, 12 in each country.

Hypothesis

We hypothesize that the combined protocol will be as effective as the standard protocol in the treatment of severe and moderate acute malnutrition as measured by recovery rate, length of stay, average weekly weight and MUAC gain, and coverage. The combined protocol will be more cost-effective than the standard protocol. Differences between the combined and standard protocols are presented in Table 2.

Study site and population

There are two sites in this multi-center cluster randomized trial: Aweil East, South Sudan and Nairobi, Kenya. Aweil East is a rural setting in the former state of Northern Bahr el Ghazal with a total population of 309,921 and an under five population of 59,574 according to the most recent national population and housing census in 2008. ACF-USA supports 16 malnutrition clinics in the area; each is approximately 20–30 km apart. At the time the study was initiated, only 12 of these clinics were supported by ACF-USA, and these 12 were all selected for inclusion in the study.

Nairobi county is an urban area with a total population of approximately 3.1 million, of which 13% are children under 5 years, according to the 2009 population census. Three sub-counties of Nairobi were selected in collaboration with the Ministry of Health (MoH) based on a high burden of malnutrition and a need for nutritional support (Embakasi North, Embakasi South and Embakasi West). Out of the 32 health facilities in the three sub-counties, 12 health facilities were selected based on the following key factors: the level of care provided (hospitals and dispensaries excluded), the type of care provided (routine child

Table 1 Nutritional protocol for the control and intervention trial arms

	Standard protocol (control)	Combined protocol (intervention)
Admission criteria	OTP • WHZ <−3 and/or • MUAC <115 mm and/or • Bilateral pitting oedema (+/++) and • Clinically uncomplicated[a] SFP • Discharged from OTP and/or • WHZ <−2 to >−3 and/or • MUAC 115 to <125 mm and • Clinically uncomplicated[a]	• MUAC <125 mm and/or • Bilateral pitting oedema (+/++) and • Clinically uncomplicated[a]
Treatment frequency	OTP Weekly SFP 14 days	MUAC <115 mm and/or oedema (+/++) MUAC 115 to <125 mm
Treatment transition criteria	▪ Child meets OTP 'cured' definition as described below	• Two consecutive MUAC measurements at or above 115 mm and • No oedema
Dosage	OTP RUTF 200 kcal/kg/day SFP RUSF 500 kcal/day (1 sachet/day)	MUAC <115 mm and/or oedema (+/++) RUTF 1000 kcal/day (2 sachets/day) MUAC 115 to <125 mm RUTF 500 kcal/day (1 sachet/day)
Cured	OTP ▪ Child maintains MUAC ≥115 mm for 2 consecutive visits[b] and/or ▪ WHZ >−3 for 2 consecutive visits[b] and ▪ No oedema for 2 consecutive visits SFP Child maintains WHZ >−2 and/or MUAC ≥125 mm for a period of 2 consecutive visits[b]	≥125 mm for 2 consecutive measurements and no oedema

[a]Clinically uncomplicated: passes the appetite test, no Integrated Management of Childhood Illness (IMCI) danger signs [11]/no serious medical complications
[b]Dependent on which criteria the child was admitted on

health services available), the population served (slum or peri-urban communities), and expected caseload of malnutrition. Each treatment facility is approximately 3–5 km apart. The clinics in Nairobi are run by the MoH, and the IRC supports with research staff at each clinic to implement the ComPAS trial.

Eligibility

Children 6–59 months with uncomplicated acute malnutrition are eligible for inclusion in the study per the following criteria:

- MUAC <125 mm

and/or

- Bilateral pitting oedema (+/++)

and

- Passes the appetite test (consumption of 30 g of RUTF within 20 min)

and

- No medical complications (i.e. no features of severe illness as defined by the Integrated Management of

Table 2 Outcomes

	Measurement variable	Analysis metric	Method of aggregation	Time point
Primary				
Recovery	MUAC ≥125 mm and no oedema	Final value	Proportion	End of treatment
Secondary				
Coverage	% of children eligible for treatment (MUAC <125 mm) who receive it	Final value	Proportion	Mid-point of study
Defaulter	Child discharged as defaulter (3 missed visits)	Final value	Proportion	End of treatment
Died	Child died during treatment	Final value	Proportion	End of treatment
Length of stay	Days in treatment	Duration of time	Sum	End of treatment
Average daily weight gain	g/kg/day	Daily	Mean	End of treatment
Average daily MUAC gain	mm/day	Daily	Mean	End of treatment

Childhood Illness (IMCI) [11], e.g. no severe nausea/ vomiting, no severe dehydration, no severe pneumonia)

A child is excluded from the study if he or she has ever been enrolled in the ComPAS trial or if he or she is receiving SAM or MAM treatment elsewhere, unless he or she was recently discharged from SAM treatment in order to attend MAM treatment.

Informed consent procedure

Consent is sought at two levels: at the level of the cluster, by the health facility officer in charge of each clinic prior to cluster randomization, and at the level of the individual, by the caretaker of each child prior to enrolment. When a caretaker arrives to any health facility included in the ComPAS trial seeking treatment for their malnourished child, they are seen by a community health or nutrition worker to confirm that they are eligible to receive treatment (i.e. they have a MUAC <125 mm, and/or a WHZ < −2, and/or oedema). Once their eligibility for treatment is confirmed, they are seen by the ComPAS research officer and clinical officer responsible for their care. First, the research officer will confirm that the present caretaker is a primary guardian for the child. If yes, the research officer describes the aims of the study as detailed in the 'participant information sheet', ensuring that the caretaker feels comfortable and understands the information. The participant information sheet provides details of the treatments provided in the study. The research officer will ensure the caretaker understands that treatment is available for all malnourished children regardless of whether they choose to participate in the study. Caretakers who agree to participate in the study will indicate their consent by signing a written consent form. If caretakers are not able to read or write, an impartial witness will oversee the consent process and attest to the caretaker's verbal consent. If the caretaker is not a primary guardian or chooses not to participate in the study, their child is enrolled for treatment only, and their information is not collected.

Randomization and blinding

Sequence generation

Randomization sequence is generated using an online sequence generator [12].

Type

There is stratification by country to ensure equal, 1:1 distribution of control and intervention clinics (clusters) in each country.

Allocation concealment mechanism and implementation

Clinics agree to participate understanding that group allocation is unknown in advance and is allocated randomly. The study statistician applies the random number sequence to a pre-written list of participating clinics, and the study team conveys the resultant allocation to the clinic staff. Individual carers attending clinics for the first time are very unlikely to know in advance whether their local clinic is in the intervention or control arm of the study.

Blinding

Due to the nature of intervention, this is not a fully blinded study. Front-line clinical and study staff must know whether they are treating children according to intervention or control (standard care) protocols, and the same staff enrol, manage and follow up patients. Staff in the standard protocol clinics were given refreshing trainings to reinforce standard protocol implementation, and staff in the combined protocol clinics were given trainings to roll out the new protocol. Staff in the clinics do not have access to overall treatment outcomes for each clinic or each arm of the trial; they are only aware of individual outcomes for the children they are responsible for treating. Similarly, individual carers cannot be blinded to the intervention being given to their child. Important to note however is that intergroup differences are unlikely to be striking to anyone but expert observers: both study arms use nutrient-dense food pastes, with RUTF and RUSF being peanut-based with similar taste and appearance; children are measured and

clinically managed in exactly the same way in both study arms. The principal investigator is blinded to the treatment outcomes, in order to maintain objective trial management and analysis of results.

Treatment

The combined protocol will be compared against the standard protocol (the national protocol in each country). The combined protocol admits all children with a MUAC <125 mm and/or oedema (+/++) and treats them according to a standardized dose of RUTF (children with a MUAC <115 mm or oedema receive 1000 kcal/day of RUTF; children with a MUAC 115 to <125 mm receive 500 kcal/day of RUTF). The combined protocol remains in line with globally accepted practice, with children recovering from SAM receiving enough therapeutic food to cover their total energy needs and children with MAM receiving a supplement to their family diet (most SFP protocols provide approximately 500–550 kcal/day of RUSF). The standard protocol includes treatment of SAM in an OTP using RUTF (200 kcal/kg/day) and MAM in a SFP using RUSF (500 kcal/day), as approved by the WHO, UNICEF, WFP and Ministries of Health in each country. The medical components of each protocol are the same, with children in the combined protocol with a MUAC <115 mm and/or oedema receiving the same systematic medications as those in the standard protocol enrolled in the OTP (per national guidelines). Children are managed at level 1 (community) health facilities by nurses or clinical officers for the medical aspects of care and by nutritionists for the nutritional components. If a child requires any additional medical care, they are seen by a nurse or clinical officer in the same facility. The few requiring higher level treatment are referred to the nearest inpatient facility. The qualifications of the staff and level of care are the same across both arms. The combined and standard nutritional treatment protocols are summarized in Table 1.

At each weekly follow-up visit, SAM cases are seen by a clinician (nurse or clinical officer) for the medical review and a nutritionist for the nutritional review. MAM cases differ in that they return for follow-up bi-weekly and receive a medical assessment only if they exhibit signs of illness or non-response to treatment. If a child has developed any medical complications or needs more specialist assessment, they are referred to the nearest inpatient facility (hospital in Nairobi, Kenya; Stabilization Centre in Aweil East, South Sudan). If a child is not gaining weight or mid-upper arm circumference appropriately, the nutritionist will discuss with a clinician based at the health facility, exploring possible underlying medical conditions, as well as counselling the caregiver to address possible contributory factors (e.g. sharing of RUTF/RUSF with other children, household food insecurity, breastfeeding for younger children). This is the same process across both arms.

Children who miss visits are followed up by a community health worker (Kenya) or community volunteer (South Sudan) to encourage caretakers to return. Children who default are followed up by a community health worker to ascertain the child's true status (cured, died or remains malnourished).

Participants will be followed up 4 months post-discharge to assess nutritional status (weight, height, MUAC and oedema), health status (any hospitalizations since discharge and morbidities in the prior 2 weeks), and breastfeeding status. The objective of the follow-up study is to assess long-term impacts of the combined protocol.

The timeline for enrolment, interventions and assessments is in Fig. 2.

Outcomes

The primary outcome, 'recovery', in both the control and intervention groups is defined as two consecutive measurements with a MUAC ≥125 mm and no oedema. The secondary outcomes include coverage, rates of defaulting and death, length of stay, and average daily weight and MUAC gain. Cost-effectiveness will be assessed through an economic analysis of financial data following the study. The outcome metrics are described in Table 2.

Quality control and supervision

A research officer is based in each of the 24 clinics included in this study. Each research officer oversees the consent process, enrolment and treatment of children according to the study protocol and data management. They participate in initial and refresher trainings with health facility staff as well as provide continuous on-the-job trainings to clinicians and community health volunteers involved in administering treatment according to the study protocol. They assess the accuracy of anthropometric measurements taken by health facility staff and review the patient cards and registers on a daily basis to ensure data quality.

Research officers are supervised by a team of roving senior supervisors, including senior research officers, deputy manager, research field coordinator and the nutrition coordinator.

Data collection and management

In Kenya, patient anthropometry data is immediately transcribed from paper patient cards by the research officer based at the clinic using a digital data collection application (CommCare HQ; https://www.commcarehq.org) on Wi-Fi- and SIM card-enabled 7-in. Samsung Galaxy Tab A tablets. Due to Internet connectivity challenges in South Sudan, patient information is collected on paper first and later transferred to a 9.6-in. Samsung Galaxy Tab E tablet by a central data entry clerk. Data is reviewed weekly by the field coordinators and any discrepancies corrected and

	Baseline	Admission visit	Follow-up visits	Discharge visit	4-month post-discharge visit
Health facility informed consent	x				
Randomization of clusters	x				
Eligibility screen		x			
Individual Informed consent		x			
Demographic data		x			
Nutritional and medical assessment		x	x	x	x
Discharge questionnaire				x	
ASSESSMENTS		Start of study	Mid-Study	End of study	
Mid-term safety review			x		
SQUEAC coverage assessments			x		
Costing accounting data				x	
Adverse event monitoring		x	x	x	x

Fig. 2 Schedule of enrolment, interventions and assessments

recorded using a digital 'data error correction form'. In addition to the primary and secondary outcomes listed in Table 2, additional information is collected from the caregiver on morbidity, breastfeeding, protocol adherence, food security, hygiene and sanitation, caretaker education and demographic characteristics.

The procedures for assessing child anthropometry (weight, height, MUAC and oedema) are detailed in Additional file 1.

Analysis

Sample size calculation was determined using an expected recovery rate of 85% based on the average programme statistics provided by the MoH in Nairobi, Kenya, and Action Against Hunger in Aweil East, South Sudan. If the combined protocol is non-inferior to the current protocol, allowing for a 10% non-inferiority margin, then we require 12 clusters in each arm with 100 children in each cluster to demonstrate non-inferiority of the combined protocol, with 80% power at the 5% level of significance. An intra-cluster correlation coefficient (ICC) of 0.05 was assumed, a conservative estimate based on the results of a similar cluster randomized study testing an integrated SAM/MAM protocol in Sierra Leone [7]. In order to account for losses to follow-up (estimated as 15%) and cross-overs (estimated as 5% in each arm), 150 children per cluster will be recruited for inclusion in the study. The cluster size calculation is as follows: $100 \times 1/(1-0.15) \times (1/(1-0.05-0.05)^2)=146$. Therefore, with a cluster size of 150, and 24 clusters, 3600 children in total will be recruited in this study (1800 in each country).

Statistical analysis will be conducted at the individual level with appropriate adjustment for clustering within 24 clusters. Descriptive summaries of participant characteristics by arm will be tabulated. Descriptive statistics for continuous variables will include the mean, standard deviation, median, range and the number of observations. Categorical variables will be presented as numbers and percentages. The main analysis of the primary and secondary outcomes will be per-protocol given that this is a non-inferiority trial. Additionally, intention-to-treat analyses will be presented. Analyses are described in Fig. 3.

Ethics

Confidentiality

If a caretaker consents for their child to be enrolled, they are issued a ComPAS ID number, which is affixed to their paper forms and entered in digital forms. All patient forms are maintained securely in a locked file throughout the study to ensure patient confidentiality. In Kenya, data collection tablets are password protected and research officers are assigned individual logins and passwords to access the digital data collection application (CommCare). Research officers are able to enter data for patients at their assigned facility only. After, the entered data is synced online to the

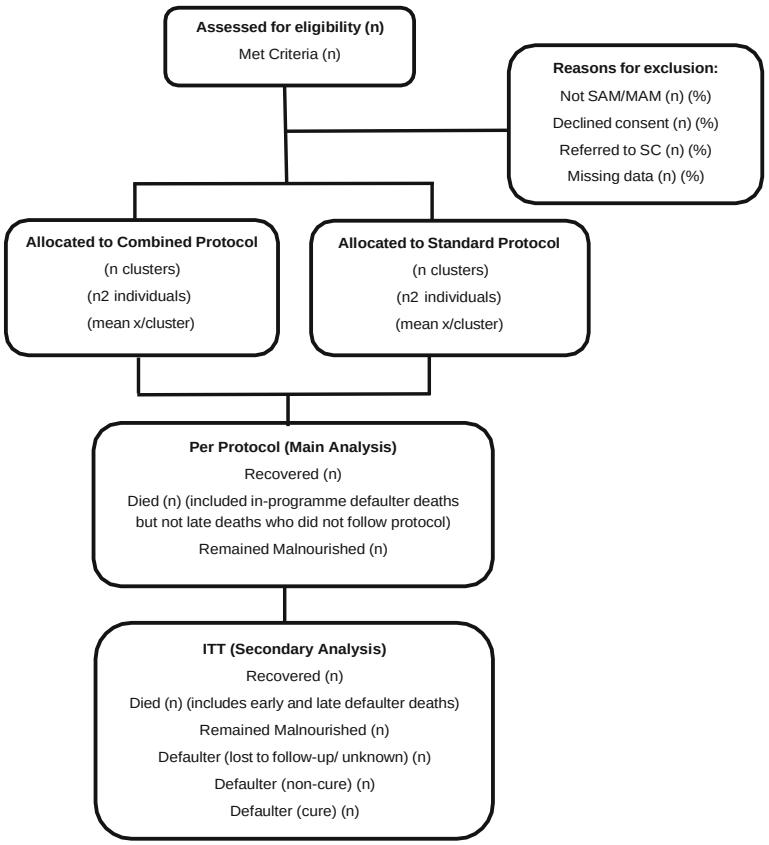

Fig. 3 Analysis flow chart

CommCare platform, which occurs daily. Research officers cannot update prior entries unless they use an approved data error correction form. They are able to view a very limited selection of historical data for the purpose of patient identification and missed visit tracking. In South Sudan, data entry tablets are password protected and data entry clerks based in the ACF office have exclusive access to CommCare using individual logins.

Safety

Adverse events, including hospitalizations and deaths, are monitored and recorded by the research team for review by the independent trial safety committee (described in the 'Trial governance' section).

Ethical approval

This study protocol was approved by the following ethical review committees:

1. Kenya Medical Research Institute (KEMRI), Nairobi, Kenya. Reference: Non-KEMRI 551
2. Ministry of Health, Juba, South Sudan. Approved 21 November 2016
3. London School of Hygiene and Tropical Medicine, London, UK. Reference: 11826

Trial governance

ComPAS is a research consortium of the International Rescue Committee, Action Against Hunger and the London School of Hygiene and Tropical Medicine. The trial is guided by a scientific committee of experts in paediatrics, humanitarian nutrition and epidemiology from the London School of Hygiene and Tropical Medicine, Washington University School of Medicine and the University of Copenhagen/University of Tampere. A trial safety committee, comprising an independent chair and a statistician from the London School of Hygiene and Tropical Medicine, will review the study outcomes and adverse events at the mid-point of the trial.

This trial is registered as ISRCTN30393230, 16 March 2017 (Additional file 2).

Discussion

This study, a multi-site cluster randomized non-inferiority trial, expected to be completed by mid-2018, is evaluating the effectiveness of a simplified and combined treatment protocol for SAM and MAM against the standard protocol

of separate products (RUTF, RUSF) and programmes (OTP, SFP) for SAM and MAM. If the results show that the combined protocol has non-inferior recovery rates compared to the standard protocol, this study will contribute to the evidence that current CMAM protocols can be simplified and that treatment of SAM and MAM can be combined (one product, one protocol and one anthropometric criterion for admission and discharge). This would make it easier for health care providers to offer treatment, reaching more children at an earlier stage before they deteriorate into severe malnutrition. The results of this trial should be interpreted together with the cost-effectiveness analysis to support policy decisions aimed at improving the coverage and quality of treatment.

Trial status

Recruitment of trial participants began on 15 May 2017 and is expected to be completed by 1 June 2018, at which point data will be analysed. The SQUEAC coverage assessments will be complete in both countries by 25 February 2018.

Additional files

Additional file 1: Procedures for taking anthropometric measurements. (DOCX 14 kb)

Additional file 2: SPIRIT checklist. (DOCX 52 kb)

Abbreviations

ACF: Action Against Hunger; CMAM: Community-based management of acute malnutrition; ComPAS: Combined Protocol for Acute Malnutrition Study; CSB++: Corn soy blend ++ (fortified); IRC: International Rescue Committee; ITT: Intention-to-treat; MAM: Moderate acute malnutrition; MSF: Médecins Sans Frontières; MUAC: Mid-upper arm circumference; OTP: Outpatient therapeutic programme; RUSF: Ready-to-use supplementary food; RUTF: Ready-to-use therapeutic food; SAM: Severe acute malnutrition; SC: Stabilization Centre; SFP: Supplementary feeding programme; SQUEAC: Semi-quantitative evaluation of access and coverage; UNICEF: United Nations International Children's Fund; WFP: World Food Programme; WHO: World Health Organization

Acknowledgements

We acknowledge the important contributions of the study participants and their families, the Ministries of Health in Kenya and in South Sudan, the UNICEF and WFP offices in Kenya and South Sudan, and the teams of dedicated staff who provide treatment to malnourished children across all the study clinics.

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Availability of data and materials

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' contributions

JB, MK, AB, MM, CO and BM conceived and designed the study. JB, NL, BM and PO are managing the data collection. PO, NL and LH advised on specific aspects of the study protocol. JB wrote the first draft of the manuscript. All authors contributed to the writing of the final version of the manuscript and have read and approved it.

Ethics approval and consent to participate

The ComPAS trial was approved by the Kenya Medical Research Institute (KEMRI) (5 January 2017, ref: 551), the Ministry of Health Internal Review Board, South Sudan (21 November 2016) and the London School of Hygiene and Tropical Medicine, London, UK (28 November 2016, ref: 11826). Informed written consent is obtained prior to all surveys and interviews.

Competing interests

The authors declare that they have no competing interests.

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3.5 Summary of methods for objective 3

Following completion of the RCT, I conducted a secondary analysis on the intention-to-treat dataset from the ComPAS trial. This dataset included 4,078 children aged 6 to 59 months with uncomplicated severe and moderate acute malnutrition treated in Kenya and South Sudan. The analysis assessed outcomes and response to treatment and the impact of different dosage protocols for children with a severely low MUAC (<11.5 cm), severely low WAZ (<-3.0), or both.

A full description of the methods used in this analysis are available in **Paper IV.**

Chapter 4: Results

4.1 Paper II: Results for Objective 1

Paper II: Chase RP, Kerac M, Grant A, Manary M, Briend A, Opondo C, **Bailey J.** Acute malnutrition recovery energy requirements based on mid-upper arm circumference: Secondary analysis of feeding program data from 5 countries, Combined Protocol for Acute Malnutrition Study (ComPAS) Stage 1. PLoS One. 2020;15(6):e0230452. https://doi.org/10.1371/journal.pone.0230452.

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Student ID Number	173611	**Title**	Ms.
First Name(s)	Jeanette		
Surname/Family Name	Bailey		
Thesis Title	Simplified, combined protocol for acute malnutrition in children 6-59 months: the ComPAS randomized controlled trial		
Primary Supervisor	Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS One: Chase RP, Kerac M, Grant A, Manary M, Briend A, Opondo C, Bailey J. Acute malnutrition recovery energy requirements based on mid-upper arm circumference: Secondary analysis of feeding program data from 5 countries, Combined Protocol for Acute Malnutrition Study (ComPAS) Stage 1. PLoS One. 2020;15(6):e0230452. https://doi.org/10.1371/journal.pone.0230452.		
When was the work published?	June 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This paper describes the results from the first stage of the ComPAS research- a secondary analysis of routine program data. I came up with the idea for this analysis and formulated the research questions, obtained funding and managed the research as the principal investigator. I worked closely with the statistician for stage 1, Dr. Rachel Chase, to organize, review and interpret the data. Dr. Chase cleaned and analyzed the stage 1 dataset and developed the methods to achieve the objectives of the analysis plan I developed, in close consultation with myself, Dr. Kerac and Dr. Opondo. I wrote the first full draft of this article. Dr. Chase developed the graphs and figures and revised the manuscript. Dr. Chase and I worked together to further revise the paper, manage inputs from co-authors, respond to peer reviewer comments and finalize the paper for publication. *Note: As the PI for the overall ComPAS project with multiple sub-studies, I felt it was important to build a research team that shared credit for key pieces of work. For this reason and because I did not conduct the analyses myself, I thought it was appropriate for first authorship to go to the statistician Dr. Chase and I took on the senior authorship. This paper is included in my thesis because it represents the foundational research work I did for my PhD.

SECTION E

Student Signature	Jeanette Bailey
Date	1 April 2021

Supervisor Signature	Dr Marko Kerac
Date	15/4/2021

PLOS ONE

RESEARCH ARTICLE

Acute malnutrition recovery energy requirements based on mid-upper arm circumference: Secondary analysis of feeding program data from 5 countries, Combined Protocol for Acute Malnutrition Study (ComPAS) Stage 1

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Abstract

Background

Severe and moderate acute malnutrition (SAM and MAM) are currently treated with different food products in separate treatment programs. The development of a unified and simplified treatment protocol using a single food product aims to increase treatment program efficiency and effectiveness. This study, the first stage of the ComPAS trial, sought to assess rate of growth and energy requirements among children recovering from acute malnutrition in order to design a simplified, MUAC-based dosage protocol.

Methods

We obtained secondary data from patient cards of children aged 6–59 months recovering from SAM in outpatient therapeutic feeding programs (TFPs) and from MAM in supplementary feeding programs (SFPs) in five countries in Africa and Asia. We used local polynomial smoothing to assess changes in MUAC and proportional weight gain between clinic visits and assessed their normalized differences for a non-zero linear trend. We estimated energy needs to meet or exceed the growth observed in 95% of visits.

request form can accessed here: https://datacompass.lshtm.ac.uk/cgi/request_doc?docid=8391. The online request process ensures all requests are seen and addressed immediately. For questions, the study team can be contacted at airbel@rescue.org.

Funding: ComPAS Stage 1 was funded by Office of US Foreign Disaster Assistance (OFDA website: https://www.usaid.gov/who-we-are/organization/bureaus/bureau-democracy-conflict-and-humanitarian-assistance/office-us), grant number AID-OFDA-G-14-00208, awarded to the International Rescue Committee (JB's affiliation). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Results

This analysis used data from 5518 patients representing 33942 visits. Growth trends in MUAC and proportional weight gain were not significantly different, each lower at higher MUAC values: MUAC growth averaged 2mm/week at lower MUACs (100 to <110mm) and 1mm/week at higher MUACs (120mm to <125mm); and proportional weight gain declined from 3.9g/kg/day to 2.4g/kg/day across the same MUAC values. In 95% of visits by children with a MUAC 100mm to <125mm who were successfully treated, energy needs could be met or exceeded with 1,000 kilocalories a day.

Conclusion

Two 92g sachets of Ready-to-Use Therapeutic Food (RUTF) (1,000kcal total) is proposed to meet the estimated total energy requirements of children with a MUAC 100mm to <115mm, and one 92g sachet of RUTF (500kcal) is proposed to meet half the energy requirements of children with a MUAC of 115 to <125mm. A simplified, combined protocol may enable a more holistic continuum of care, potentially contributing to increased coverage for children suffering from acute malnutrition.

Introduction

Acute malnutrition (AM) is divided into Severe Acute Malnutrition (SAM) and Moderate Acute Malnutrition (MAM), with SAM defined as a MUAC <115mm, weight-for-height z-scores below -3 of the median WHO growth standards or by the presence of nutritional oedema, and MAM defined as MUAC 115 to <125mm or weight-for-height z-scores of between <-2 and ≥-3. Globally, at any one time, it is estimated that more than 50 million children under the age of five suffer from acute malnutrition (AM) [1], likely translating to over 100 million incident cases of SAM each year [2–5]. SAM accounts for approximately 516,000 deaths annually, MAM for 359,000 [6,7].

Currently, SAM and MAM are treated in separate feeding programs, with separate protocols, products, and supply chains [8]. Resource constraints and logistical challenges often result in SAM being prioritized due to its particularly high case-fatality and long-term adverse outcomes [9,10]. MAM services are often unavailable or time-bound (e.g. only present during the 'hungry' season or in times of food crisis). Increasing evidence suggests that this is an important gap: children with MAM-associated anthropometric deficits (a weight-for-height z-score between -3 and <-2) are 3 times more likely to die than healthy children [11], and prevalence of MAM can affect the incidence and severity of SAM [12,13].

To better tackle both MAM and SAM, there is growing momentum within the nutrition community to view the two as a continuum condition rather than as two distinct states [14–17]. Thus simplifying and unifying the treatment protocols might ease integration into existing health services, increase treatment coverage, and potentially enhance cost-effectiveness by treating MAM earlier and more easily, preventing costly and dangerous SAM [15,16,18]. Early data on such programming is promising [18]. However, to inform future policy decisions, stronger evidence is needed [19].

Two questions are key. First, can mid-upper arm circumference (MUAC) be used as the primary anthropometric indicator for screening, treatment, and discharge of uncomplicated cases of acute malnutrition? MUAC-only programming offers many practical and logistical advantages over weight-for-height [20]. MUAC for admission has been found to detect the

highest-risk children [21,22]. However, further evidence is needed on MUAC as a patient monitoring and discharge criterion. In particular, does MUAC reflect similar trends as weight gain in response to nutritional treatment [23–25]?

Second, how much energy is needed to most efficiently treat acute malnutrition? A wide variety of products and approaches are available for addressing MAM, not only limited to treatment [14,26,27]. Studies show that nutrient-dense pastes (Ready-to-Use Therapeutic Food, or RUTF) that are typically recommended for treatment of SAM result in higher recovery rates for MAM patients than do fortified blended flours [28–34]. For SAM, RUTF is standard and is prescribed to provide 175–200 kcal/kg/day [35,36]. This energy dosage is high because it is based on inpatient-focused models of care where expected patient weight gain was high: 10–15 g/kg/day [37]. In contrast, expected weight gain in today's outpatient-focused programmes is about 4.5 to 6.8 g/kg/day [38]. Children may not thus require all the energy they are prescribed, especially as growth slows towards the end of treatment [39–42].

We aimed to address these evidence gaps by assessing MUAC and proportional weight gain, and estimating energy needs of children as they recover from SAM and MAM. The overall aim of this ComPAS Stage 1 study was to design a simplified, MUAC-based dosage protocol and statistically assess its theoretical performance providing adequate energy. Driven initially by an immediate need to inform a cluster-randomised control trial on a "Combined Protocol for Acute Malnutrition Study" (ComPAS study) [43], our goal has been to inform and ultimately improve wider SAM/MAM programming. Specific objectives are threefold. First, we aim to describe and compare MUAC and weight gain trends in children being treated for acute malnutrition to assess if MUAC is a valid proxy of proportional weight gain during treatment. Second, we will calculate energy requirements needed to support observed weight and MUAC gain in children recovering from acute malnutrition and to explore any differences by age and by MUAC category (SAM vs MAM). Third, we will assess the ability of a simplified MUAC-based dosage protocol to provide energy sufficient to meet estimated needs of children recovering from acute malnutrition.

Methods

Study design

This study was a secondary analysis of routine clinical data obtained from therapeutic and supplementary feeding programs (TFP and SFP, respectively).

Setting and study sample

We analyzed data from programmes run by Médecins Sans Frontières (MSF-France) in South Sudan in 2010; Action Against Hunger (AAH-USA) in Pakistan in 2012; and International Rescue Committee (IRC) in Chad (2013 & 2014), Kenya (2012, 2013, & 2014), and Yemen (2014) as these programs had treatment data (rather than survey or cross-sectional data) and a partnership to do this research. Admission of children to these outpatient TFPs for SAM or SFPs for MAM were based on screenings in the community or directly at the health centre. Admission criteria for both TFPs and SFPs followed standard international criteria, as laid out in national acute malnutrition treatment protocols in use at the time in that particular country [44–47]. Enrolled patients had to be clinically well, alert and demonstrate appetite. Acute malnutrition cases eligible for treatment were enrolled in the TFP or SFP programme and monitored on a weekly basis (SAM) or a two-week basis (MAM). Therapeutic rations for SAM patients were provided based on weight (200 kcal/kg/day) and supplementary rations for MAM patients were provided as a standard ration which varied by country. Patients were discharged when they reached a combination of discharge criteria, which differed between TFP and SFP and also varied by country.

Patient data were originally available on paper-based patient monitoring cards held securely on-site at each programme. Data from the cards were entered into an Excel database between October 2014 and May 2015 using double data entry for quality control. The main study team at IRC received anonymized data and merged it into a single database stored on a password-protected institutional server. We tagged data by type of facility (TFP or SFP) and country from which the cards were obtained.

Participating children were those aged 6 to 59 months and enrolled in either outpatient TFPs for SAM or SFPs for MAM. Children were eligible for analysis if they were discharged from a feeding programme as recovered, experienced a non-negative MUAC gain, and experienced either a weight gain of at least 10% from admission to discharge if admitted as a SAM patient or at least 3% from admission to discharge if admitted as a MAM patient. By using data from patients who achieved these outcomes, trends reflect the most successful cases coming out of current TFP and SFP programs. We chose to focus on children who had achieved recovery in order to establish energy requirements for successful growth.

Exclusion criteria were those children with unusable data, defined as having no follow-up visits, or missing age, sex or date information. Data analysis was limited to MUACs 100mm to 140mm due to limited information outside these values for reliable estimates of weight change, MUAC change, and energy needs within each MUAC category.

Visits recording extreme high or low anthropometric measures which are thus likely to be measurement or recording errors were also excluded according to the following criteria [48]: weight-for-height z-score below -5 or above 5, weight-for-age z-score below -6 or above 5, height-for-age z-score below -6 or above 6, MUAC below 65mm or above 200mm, weight change of more than 25 grams per kilogram weight per day, or MUAC change in either direction of greater than 15mm per week.

Variables, measurements, and statistical methods

Variables available on the patient cards included: date of visit to clinic, age in months at admission, presence of oedema at admission, mid-upper arm circumference (MUAC) measured in millimeters (mm) at each visit, weight measured to the tenth of a kilogram (kg) at each visit, and height measured to the tenth of a centimeter (cm) at admission and discharge. Each card followed an individual child through one course of treatment. Not all children completed treatment, and registration cards could not necessarily be linked if the same child had multiple courses of treatment or obtained treatment for both SAM and MAM in separate programmes.

The total number of study participants was determined by available programme data. Because this was a secondary analysis, *a priori* sample size calculations were not done. Five different countries were included so as to represent a variety of different settings where acute malnutrition is highly prevalent.

From the total eligible sample, we used different subsamples for analyses. For polynomial smoothing used to visually compare trends in weight and MUAC change since prior visit by MUAC at prior visit, we randomly selected 1000 visits from each of the five countries from which patient cards were obtained, resulting in a single 5000-visit subsample with an equal number of observations from each country (to which Yemen could contribute the least with 1279 eligible observations). One-hundred such subsamples were used to test whether the linear trend of the difference in the normalized trends was non-zero. For theoretical assessment of the proposed therapeutic protocol, we used 100 different subsamples of 2500 visits (500 visits from each country) to simulate average performance of the protocol given varying distributions of patient visits from the sample. To estimate indicators to two significant figures, 100 resamples were sufficient.

We conducted the analysis using Stata 13.1 [49]. Weight-for-height (WHZ), weight-for-age (WAZ) and height-for-age (HAZ) z-scores were calculated at admission and discharge using the 2006 WHO child growth standards via the user-written Stata command zscore06 [50]. One-week change in MUAC was calculated as the difference between MUAC between two visits (usually one week apart). If visits were not one week apart, change was assumed constant over the period of time between visits, and so change over the course of two weeks was divided in half to reflect one-week change in measurements. Proportional weight gain was similarly assumed constant between visits, and was calculated as grams of weight gained per kilogram of weight at prior visit per day. Change in MUAC (mm/week) and proportional weight change (g/kg/day) were primary outcomes with MUAC the predictor.

Using local polynomial smoothing (via the lpoly command) with the 5000-visit subsample, we visually assessed one-week MUAC growth (mm/week) versus MUAC and proportional weight gain (g/kg/day) versus MUAC. This was done among all patients with eligible outcomes to understand whether MUAC and weight change responded similarly to treatment. A secondary analysis was performed assessing these by age group to determine if the relationships were similar for 6–11 month olds, 12–23 month olds, and 24–59 month olds. A set of 100 simulations (each with a different 5000-visit subsample as used for local polynomial smoothing) assessed via linear regression whether the difference in normalized means of MUAC growth and proportional weight gain had a non-zero trend.

Daily energy needs (kcal) were calculated as [51,52]:

$$(\text{current weight (kg)} \times \text{resting energy needs (kcal/kg/day)}) + (\text{weight gain (g)} \times \text{energy costs of weight gain (kcal/g)})$$

Resting energy needs were estimated at 82 kcal/kg/day, which is slightly more than requiredfor normal growth of children aged 6 to 12 months (see Table 3.2 and 3.3 in the Food and Agricultural Organization 2001 human energy requirements report) and consistent with prior estimates of energy requirements for maintenance among young children [52]. The energy cost to add 1 g of tissue was estimated at 5kcal based on several studies cited in the Food and Agricultural Organization 2001 report (pg 31) [51].

Energy needs to support observed growth were calculated for each patient visit as kcal/day per the above formula.

For children admitted to the clinic with SAM-associated MUACs (MUAC 100mm to <115mm) and with MAM-associated MUACs (MUAC 115mm to <125mm), the smallest amount of energy that would be sufficient to achieve observed growth in 95% of visits, i.e. the 95th percentile of their energy requirements, was calculated.

In secondary analyses, we compared the 95th percentile of energy needs by age group (6–23 months and 24–59 months), continent (Asia and Africa), and MUAC category at admission (<115mm and 115 to <125mm). We selected the above age ranges because most children who are admitted to community-based management of acute malnutrition (CMAM) programmes are between the ages of 6–23 months, and children <24 months are the most vulnerable to episodes of acute malnutrition. The comparison by MUAC category at admission could only be made over ranges of MUAC that these children had in common (110mm to <125mm) since, in general, patients with eligible outcomes who were admitted with MUAC of 115mm or above did not generally return to the clinic with a MUAC below 110mm during treatment. The 95th percentile was calculated over 5mm MUAC categories (such as MUAC 110 to <115mm). The 95th percentile of energy needs was not reported to reflect average energy needs, but the provision of energy sufficient for observed growth in 95% of patient visits in the category.

Having developed a simplified protocol based on the above analyses, we assessed its theoretical performance among 100 different subsamples of 1000 patient visits each (200 patients from each country). One-hundred simulations were found to provide similar results as 1000 simulations in initial testing, so 100 simulations were considered suitable to achieve stable results. Two-hundred patient visits were selected from each country so that the patients representing each country would vary in every subsample (Yemen had the fewest cases at 294 patients). In each of the 100 simulated trials of the protocol, we recorded performance measures among patient visits with SAM-associated MUACs (100mm to <115mm) and MAM-associated MUACS (115mm to <125mm) separately. For patient visits with SAM-associated MUACs and (separately) with MAM-associated MUACs, we estimated the median percentage of energy needs covered by the protocol. For patient visits with SAM-associated MUACs, we have reported the mean percentage of visits among the 100 subsamples in which at least 100% of energy needs to support observed growth would be provided. For patient visits with MAM-associated MUACs, we have reported the mean percentage of visits in which at least 50% of energy needs to support observed growth would be provided.

We compared how the proposed protocol would compare in terms of energy provision to other protocols: namely comparing average energy provision by MUAC from Golden's minimum (135 kcal/kg/day), intermediate (150 kcal/kg/day), and standard (170 kcal/kg/day) protocols [53]; the Sierra Leone protocol (175 kcal/kg/day if MUAC<115mm, 75 kcal/kg/day if MUAC 115mm to <125mm) [18]; and the National Guideline for Integrated Management of Acute Malnutrition for Kenya (or "Kenya protocol", 200 kcal/kg/day if admitted to SAM treatment program, 500 kcal/day if admitted to MAM treatment program) [47]. The Golden protocols call for complete energy needs to be provided through therapeutic care and provides minimum and intermediate options with lower energy provisions for resource-constrained settings. The Kenya protocol provides complete energy needs to patients with SAM until they are discharged as recovered. Like the proposed protocol, the Sierra Leone protocol and Kenya protocol provide only supplemental energy to children with MAM. The Sierra Leone protocol also uses MUAC as the primary anthropometric admission criterion, with oedema also indicating SAM treatment should be provided.

Ethical approval

Stage 1 of the ComPAS study was approved by the London School of Hygiene and Tropical Medicine ethics committee (reference number 11826).

Results

Participants

A total of 10,068 patient record cards from TFP and SFP programs in Kenya, Pakistan, Chad, Yemen, and South Sudan representing 57,138 patient visits were collected (Fig 1). Of these, we excluded 1,788 records (7,105 patient visits) from analysis due to unusable data or biologically implausible data. Of the 8,280 patient cards with usable and biologically plausible data, 5,518 patient cards (representing 33,942 visits) came from patients who ultimately had eligible outcomes.

Descriptive data

In all countries but South Sudan, there were more female patients than male patients (Table 1). In all countries, age was frequently rounded to years rather than months, resulting in imprecise age data. Most patients were under 2 years old, with 29% of patients age 6–11 months, and

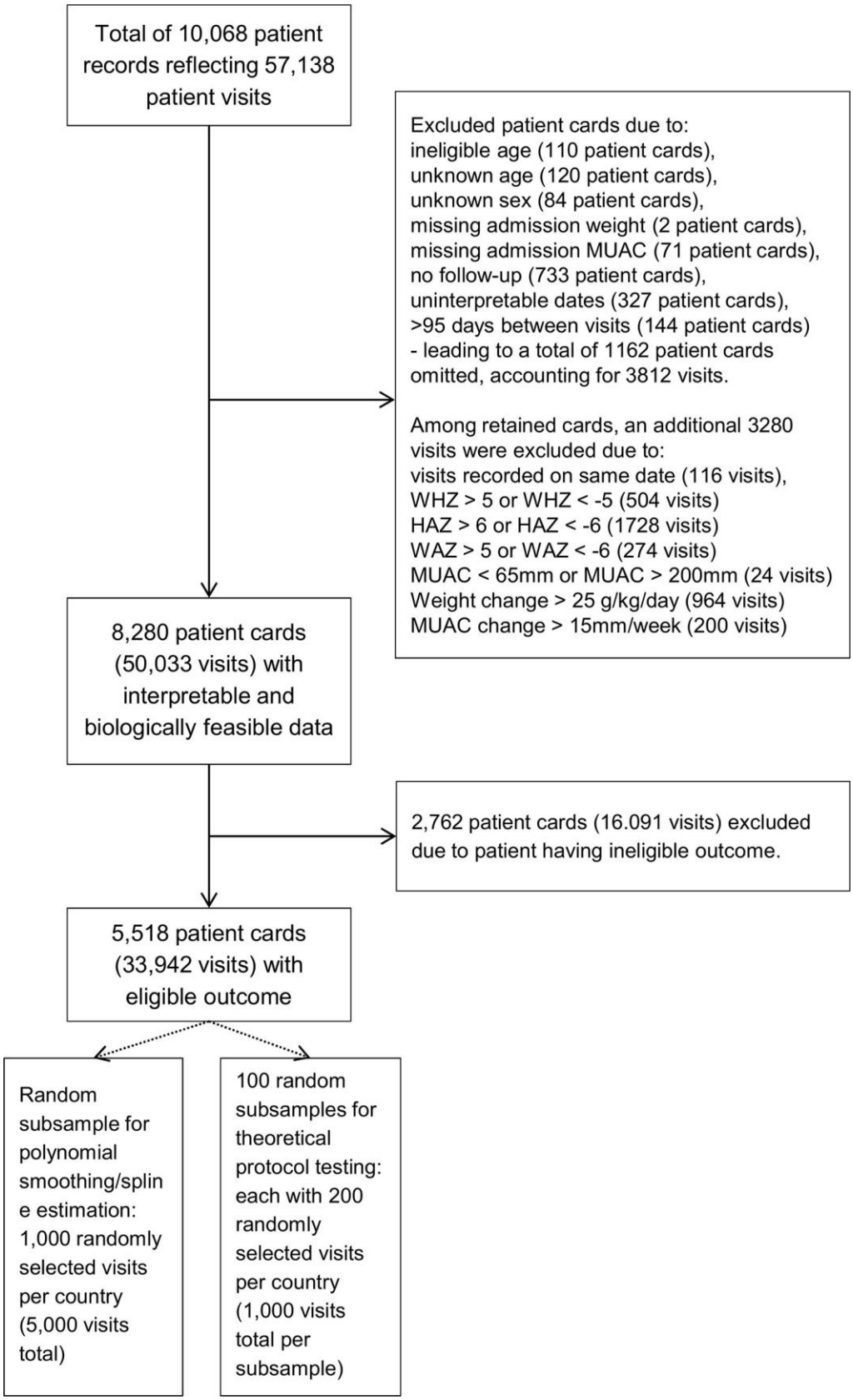

Fig 1. Study flow chart.

https://doi.org/10.1371/journal.pone.0230452.g001

Table 1. Sample description.

	Kenya	Pakistan	Chad	Yemen	S. Sudan	Total
Total number of patient cards	439	1952	1422	483	1222	5518
. . . representing X visits	2701	9052	10085	2916	9188	33942
Age group, n (%)						
6–11 months	146 (33%)	493 (25%)	548 (39%)	113 (23%)	326 (27%)	1626 (29%)
12–23 months	135 (31%)	813 (42%)	576 (41%)	128 (27%)	544 (45%)	2196 (40%)
24–35 months	77 (18%)	400 (20%)	211 (15%)	69 (14%)	248 (20%)	1005 (18%)
36–59 months	81 (18%)	246 (13%)	87 (6%)	173 (36%)	104 (9%)	691 (13%)
Sex, n (%)						
Female	226 (51%)	1104 (57%)	802 (56%)	270 (56%)	585 (48%)	2987 (54%)
Male	213 (49%)	848 (43%)	620 (44%)	213 (44%)	637 (52%)	2531 (46%)
Stunting at admission, n (%)						
HAZ<-2	206 (47%)	876 (45%)	989 (70%)	201 (42%)	484 (40%)	2756 (50%)
HAZ-2	226 (51%)	370 (19%)	429 (30%)	281 (58%)	731 (60%)	2037 (37%)
Missing height	7 (2%)	706 (36%)	4 (<1%)	1 (<1%)	7 (1%)	725 (13%)
Admitting facility, n (%)						
TFP	121 (28%)	276 (14%)	386 (27%)	116 (24%)	1222 (100%)	2121 (38%)
SFP	318 (72%)	1676 (86%)	1036 (73%)	367 (76%)	N/A	3397 (62%)
Oedema, n (%)						
Oedema = 0	239 (54%)	1943 (>99%)	1421 (>99%)	483 (100%)	3 (<1%)	4089 (74%)
Missing	200 (46%)	8 (<1%)	1 (<1%)	0 (0%)	1209 (99%)	1418 (26%)
Oedema = 1,2,or 3	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	10 (1%)	11 (<1%)

https://doi.org/10.1371/journal.pone.0230452.t001

40% age 7–23 months. In Pakistan, nearly half of patients had no height data to assess for stunting. Data on presence of oedema were almost always missing or indicative of no oedema; if all non-zero, non-missing oedema values indicated presence of oedema, 11 patients would have been recorded as having oedema, almost all in South Sudan. In South Sudan, all data were from TFP facilities treating SAM; in other countries, 67–82% of patient registration cards came from SFP facilities treating MAM.

MUAC and weight changes

Weekly MUAC change showed similar trends as proportional weight gain when assessed by MUAC (Fig 2) and were not significantly different when their values were normalized between 0 and 1 and their differences assessed for a non-zero linear trend in 100 simulations. For MUAC 100mm to <125mm, slope ranged from -0.003 to 0.002 with mean of -0.0002, with the F-test non-significant in 86% of simulations. For MUAC 125mm to 140mm, slope ranged from -0.006 to 0.001 with mean of -0.002, with the F-test non-significant in 54% of simulations (i.e., MUAC gain was slightly slower than proportional weight gain at higher MUACs in nearly half of simulations with MUAC 125mm to 140mm). Both MUAC gain and proportional weight gain were highest at lower MUACs, and declined to lower levels of growth at higher MUACs. Specifically, mean weekly MUAC change went from approximately 2mm/week at the lowest MUACs (100 to <110mm) to 1mm/week among those with MUAC 120mm to <125mm. Similarly, mean proportional weight gain declined from approximately 3.9g/kg/day to 2.4g/kg/day across the same MUAC values. An increase of 1mm MUAC was associated with a decrease in weekly MUAC growth of 0.06mm (F-test p-value<0.001) and a decrease in daily proportional weight gain of 0.05g/kg/day (F-test p-value<0.001), indicating that

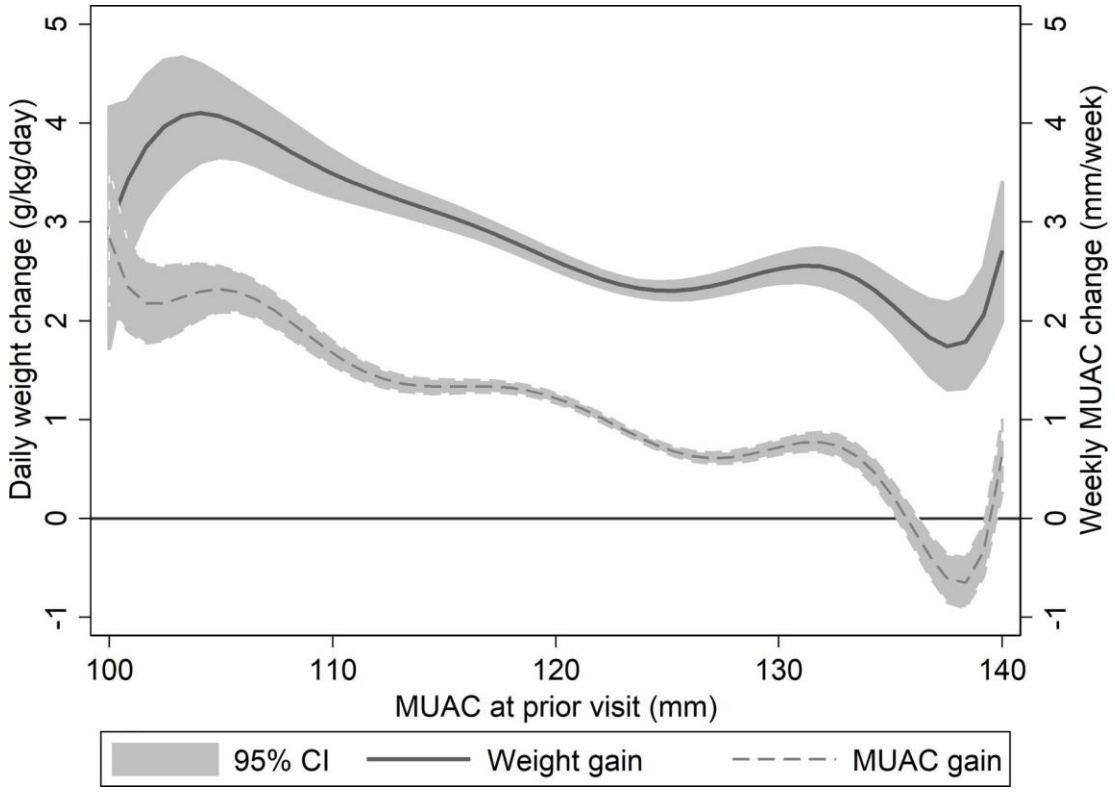

Fig 2. Average daily proportional weight change (solid line) and weekly MUAC change (dashed line) vs MUAC at prior visit.

https://doi.org/10.1371/journal.pone.0230452.g002

recovering children with higher MUACs grew more slowly according to these measures than children with lower MUACs.

Energy needs

Energy need calculations indicated that 1,000 kilocalories per day were sufficient or more than sufficient in 95% of patient visits to support the growth observed among children who ultimately achieved eligible recovery outcomes (Fig 3). However, we estimated that older children (over 24 months) with higher MAM-associated MUACs (MUAC 115mm to <125mm) needed 1200kcal per day to cover 100% of energy needs to support observed growth in 95% of visits. Children over the age of 24 months made up one-fifth of the database (Table 1) and, of these, nearly all had MUACs above 115mm throughout treatment. While we estimated that most of these visits (83%) needed 1,000 kilocalories or fewer to meet their daily energy needs, this fell short of the 95% goal set for this protocol.

We noted differences in the 95th percentile of daily energy needs among children with MUAC < 115mm MUACs in Asia versus Africa, with children in African countries needing 960kcal/day versus 810kcal/day in Asia (Fig 3); however, the difference was smaller among children with MUACs 115mm to <125mm in these two regions (approximately 1050kcal/day in Africa and 995kcal/day in Asia). These results are consistent with other studies indicating that children in Asia with SAM are different from those in Africa, with a comparatively high proportion of recovery and low mortality even in the absence of intensive treatment [54].

Comparing children admitted with SAM-associated MUACs (100mm to <115mm) to those admitted with MAM-associated MUACs (115mm to <125mm), estimated energy needs

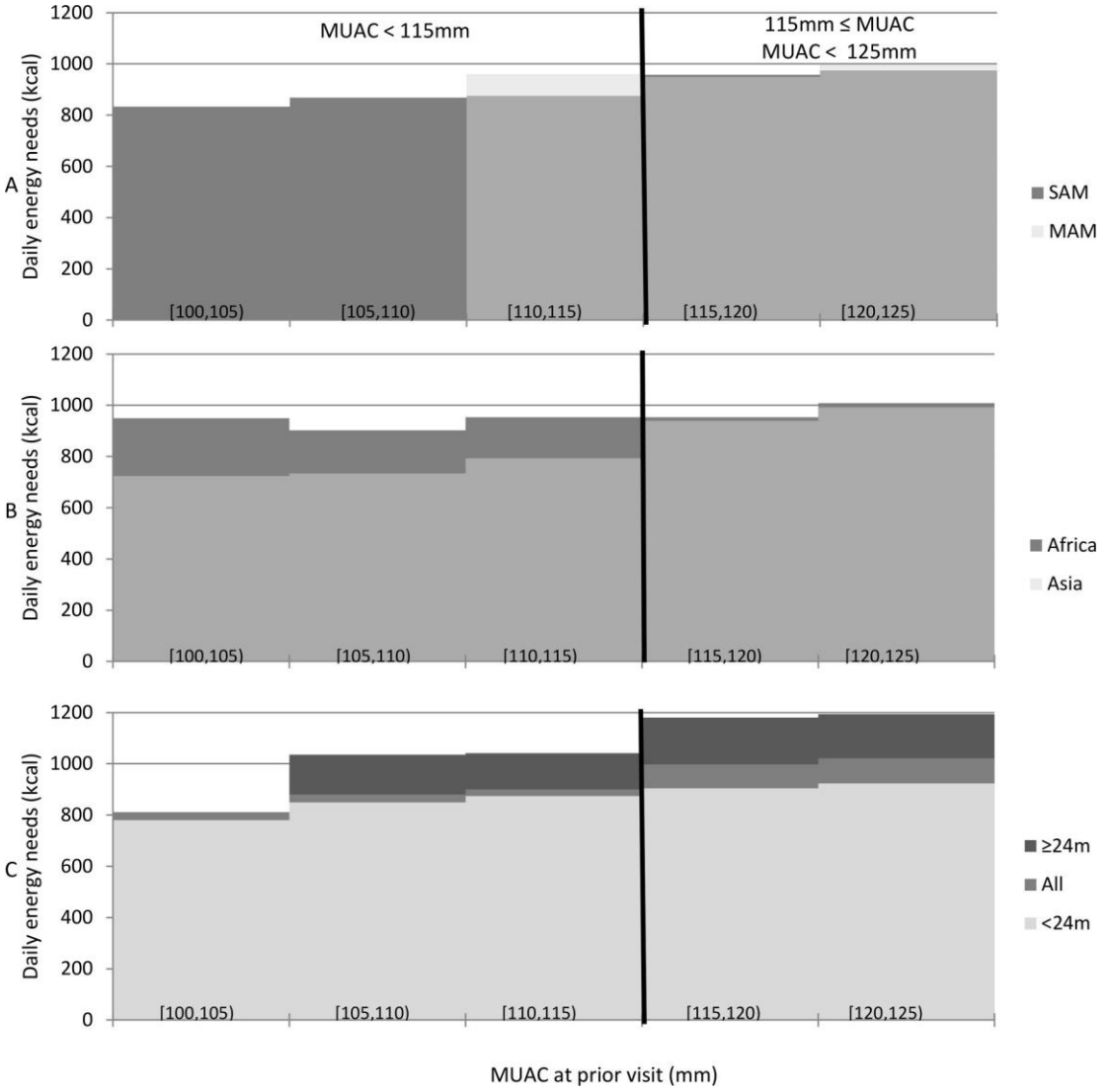

Fig 3. Estimated daily energy (kcal) that would provide 95% of patient visits in the specified MUAC category with energy needs for observed growth. Comparisons are made by: (A) MUAC category at admission, (B) continent, (C) and age group of 6–23 months (<24m) or 24–59 months (≥24m).

https://doi.org/10.1371/journal.pone.0230452.g003

did not differ greatly. The 95th percentile of daily energy needs among children admitted with MAM-associated MUACs was estimated to be 1020 kcal/day; among children admitted with SAM-associated MUACs, 960 kcal/day.

Performance of a simplified, combined protocol

From the above, it appears that most children's energy needs for recovery from acute malnutrition would be covered by a protocol providing 1000 kcal/day for children with SAM, whose MUAC is 100mm to <115mm and 500kcal/day for children with MAM, whose MUAC is 115mm to <125mm. That would be equivalent to two sachets per day of RUTF for children with SAM-associated MUACs, aiming to provide 100% of daily energy needs; and equivalent to one sachet per day of RUTF for children with MAM-associated MUACs and aiming to provide 50% of daily energy needs, the remainder coming from home foods [27].

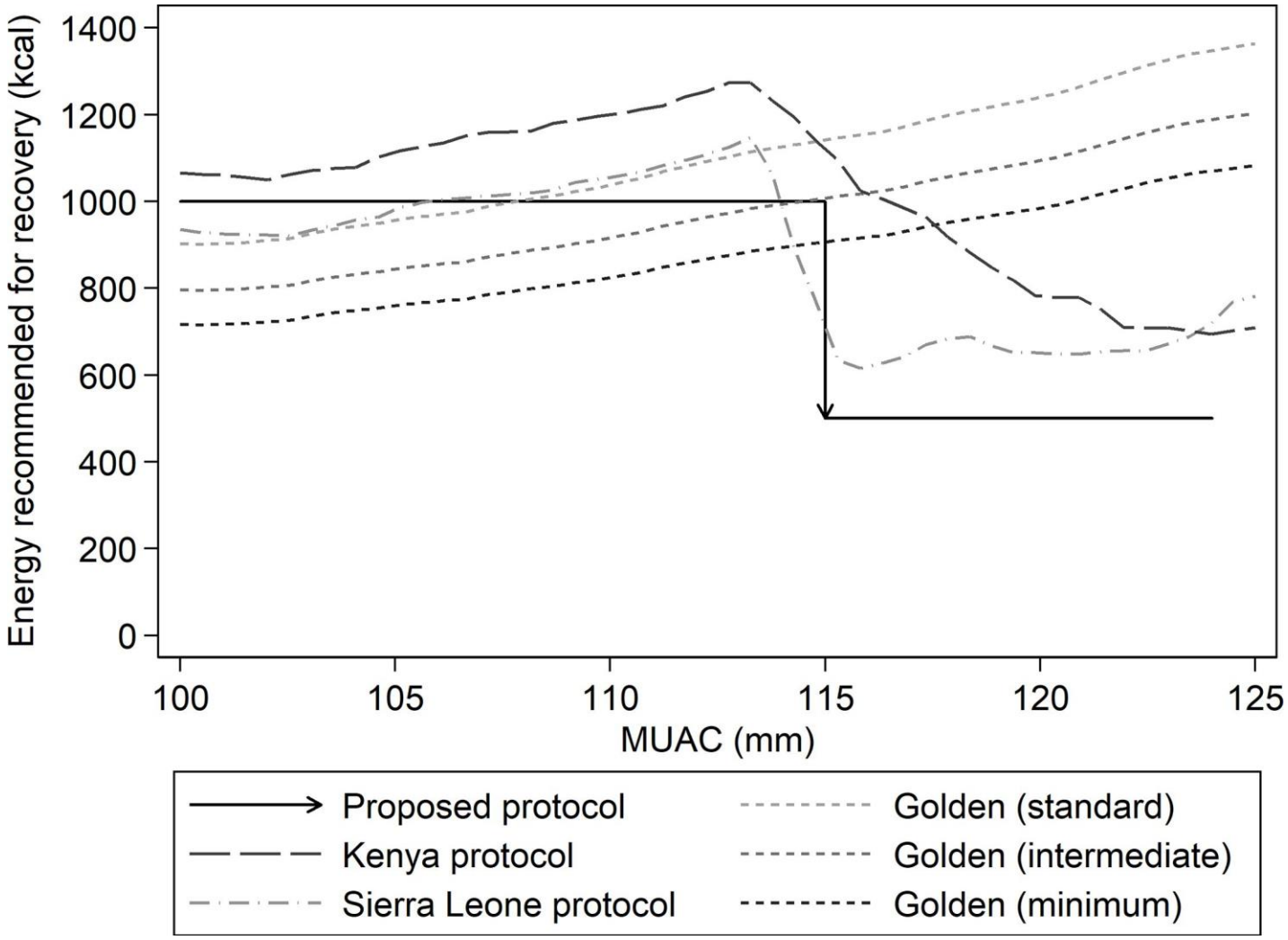

Fig 4. Comparison of mean energy provided by each of five protocols: The protocol proposed herein, Golden's minimum, intermediate, and standard protocols, the Sierra Leone protocol, and the Kenya protocol.

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Fig 4 shows how the proposed protocol would compare in terms of energy provision to other protocols. For lower MUACs (100mm to <115mm), the proposed protocol provides more calories than Golden's minimum and intermediate protocols, similar kilocalories as Golden's standard and the Sierra Leone protocol, and less than the Kenya protocol. At higher MUACs (115mm to <125mm), the proposed protocol provides approximately 100–800 fewer kilocalories per day than other protocols.

Table 2 shows the proportions of clinic visits in which the proposed protocol would provide at least 100% of estimated energy needs for children with MUAC < 115mm and at least 50% of estimated energy needs for children with MUAC 115mm to <125mm in 100 simulated trials using subsamples of 1000 visits (200 from each country) per trial. Overall, we found the protocol to be adequate for both male and female patients presenting with MAM and SAM, for children in Africa and Asia, and in each of the five countries. There were however subgroups whose energy needs were met in less than 95% of visits: older children (ages 24 to 59 months) and larger children (weights ≥ 8.0 kg). Among the older children with the lowest MUACs (age 24 to 59 months, MUAC < 115mm), total energy needs were met on an average

Table 2. Estimated energy provided by proposed protocol as percentage of energy needed in observational data using 100 trials using subsamples of 200 visits from each of five countries (1000 visits total per simulated trial).

	Visits where MUAC < 115mm				Visits where 115mm ≥ MUAC < 125mm			
Factor	Mean N (min-max)	Estimated median percentage of energy needs provided by proposed protocol	Mean percentage of visits with all energy requirements provided by protocol (Target: at least 95%)	Minimum and maximum value among subsamples	Mean N (min-max)	Estimated median percentage of energy needs provided by proposed protocol	Mean percentage of visits with half of energy requirements provided by protocol (Target: approx. 95%)	Minimum and maximum value among subsamples
Total	199 (173–225)	166%	97%	94%-100%	801 (775–827)	73%	94%	92%-95%
Sex								
Female	125 (100–148)	168%	97%	95%-100%	432 (400–471)	75%	95%	92%-97%
Male	74 (59–94)	161%	96%	89%-100%	369 (331–401)	71%	92%	88%-95%
Age (in months)								
6 to 11	115 (92–138)	175%	98%	95%-100%	291 (265–335)	83%	98%	97%-100%
12 to 23	67 (49–89)	159%	96%	87%-100%	315 (270–349)	72%	96%	93%-98%
24 to 59	17 (8–29)	133%	90%	72%-100%	191 (156–220)	60%	83%	77%-88%
Weight								
3.5 to 5.9	86 (63–109)	183%	99%	95%-100%	103 (78–130)	91%	99%	97%-100%
6.0 to 7.9	106 (85–126)	157%	96%	90%-100%	470 (435–514)	77%	97%	95%-99%
8.0 to 17.5	8 (2–14)	123%	83%	50%-100%	228 (189–263)	61%	84%	79%-90%
Admission type								
SFP	See note[◆]				453 (426–485)	74%	95%	93%-97%
TFP	195 (164–222)	166%	97%	94%-100%	347 (313–378)	72%	91%	88%-94%
Continent								
Asia	59 (41–72)	171%	99%	95%-100%	341 (328–359)	71%	94%	91%-96%
Africa	140 (116–162)	163%	96%	92%- 99%	460 (438–484)	75%	93%	90%-96%

[◆]Among eligible patients, children who were admitted to SFP facilities seldom had MUAC below 115mm during treatment and therefore performance based on TFP vs SFP admission among children with the lowest MUACs could not be compared.

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of 90% of visits (range across simulated trials 72%-100%). Among the largest children with the lowest MUACs, their total energy needs were met on an average of 83% of visits (range 50%-100%). Estimates for these groups were not reliable due to only 1–2% of visits coming from children fitting this description and each subsample having 2 to 29 such visits to assess. For older children with higher MUACs (115mm ≥ MUAC < 125mm), an average of 83% (range 77%-88%) of visits would have had at least 50% of energy needs met by this protocol in the simulated trials. Similarly, among visits from larger children (weight ≥ 8kgs) with higher MUACs, an average of 84% (range 79%-90%) had half or more of their energy needs covered. Children with higher MUACs who were age 24 months or older and/or weighed 8kgs or more made up about one-fifth of the 5,518 patients in the sample. In both cases, these values might be far enough from the goal of 95% to warrant special consideration for these groups in the development of a simplified protocol.

Discussion

Key results

We assessed how children who successfully completed a course of treatment through an TFP or SFP facility grew during their treatment, evaluating growth by the child's MUAC at their prior clinic visit. Growth trends in MUAC mirrored those of proportional weight gain. Rate of proportional weight and MUAC gain slow at higher MUAC values. Though absolute energy requirements continue to increase as children gain weight, children with higher MUAC measurements need less supplemental energy per kilogram of body weight than those with lower MUAC measurements. According to energy estimates in this study, 1000kcal per day is hypothetically sufficient to achieve the goal of covering total energy needs 95% of the time for children with a MUAC 100mm to <115mm. For children with a MUAC 115mm-<125mm, 500kcal per day would be sufficient to supplement the family diet. The protocol met energy needs in simulated statistical tests among most subgroups (males and females, each country and continent, and both admission types), and fell slightly short of these goals among the oldest children (age 25–60 months) and the heaviest children (over 8kg).

Interpretive considerations

This study used observational data from outpatient feeding programs in five countries in Africa and Asia, leveraging existing operational data to inform future studies and protocol development efforts. We compared MUAC and proportional weight gain as well as estimated the energy needs of patients who recovered from these programs. This information allowed us to formulate and theoretically test a simplified protocol.

Our limitations center around having retrospective data from routine clinical records rather than intervention data from a tightly controlled research setting. Records for the same children treated twice in the same program or treated for both SAM and MAM could not be connected. We were not able to account for possible confounders such as breastfeeding and socioeconomic status. We also excluded data points because of incomplete and inaccurate data collection, and used imprecise age data that were often rounded to the nearest year. As in any observational study, observed associations cannot infer causality. We calculated energy requirements to achieve observed growth using an evidence-based- but still theoretical—equation, not by controlled dosage tests. We cannot say what actual child energy intake was during the course of treatment. We also cannot say how children might have grown on different feeding regimes. Though RUTF dosages for children with SAM are relatively standard in TFPs worldwide, SFP rations vary and we did not have information on the exact type and amount of supplementary food given to children with MAM in SFP programs (possibilities include

ready-to-use supplementary food and different varieties of fortified blended flours). Even if exact programme details been known, exact food/energy intake of patients was not measured and is unknown.

Another limitation arose from having very few children in some subcategories (e.g. typically fewer than 20 patients over 24 months old with SAM-associated MUACs per subsample). Therefore, we could not assess the proposed protocol's theoretical performance for all subgroups that might be of interest to practitioners. This is not a major problem given that our programmes are representative of many others which also have most children younger than 24 months and lighter than 8kg. Care must be taken when extrapolating beyond children <24 months and <8kg.

Variations in completeness of data from the different country sources was expected. To minimize bias, the analysis was based on data that were most consistently available from all five countries. For example, because height data were missing from nearly half the cases in Pakistan, height was not used in the primary analysis, nor were height-based values such as stunting status and weight for height z-scores (WHZ).

Limiting our sample to those children with successful treatment outcomes allowed us to determine a theoretically sufficient amount of energy that would support observed growth in almost all cases represented in this sample. This analysis does not address how those children came to achieve that growth nor how children who did not successfully recover fared.

Finally, growth curves do not average the courses of individual children, but how much children tended to grow between visits given their MUAC at their prior clinic visit.

Generalisability

These data represented growth among children age 6–59 months in standard treatment programs in five countries in Africa and Asia. The data represent very different operational contexts. The age and anthropometric characteristics of the children included in this study reflect the reality of admissions in CMAM programs globally. However, the results should not be extended to groups for which we did not have adequate data to assess, such as older and larger children with SAM and children with very low (<100mm) MUAC.

Interpretation

This study considered the rate of weight and MUAC gain and energy needs of children with acute malnutrition as defined by MUAC status. We found that 1000 kcal/day (equivalent to two RUTF sachets per day) should meet the total energy requirements of children with a MUAC of 100mm to <115mm more than 95% of the time; 500kcal (equivalent to one RUTF sachet per day) meets half the energy requirements of children with a MUAC 115 to <125mm 95% of the time. Even among the subgroups of older and larger children that did not have these goals met 95% of the time, the protocol was estimated to meet their needs approximately 83% of the time. This protocol remains in line with globally accepted practice in which children recovering from SAM receive enough therapeutic food to cover their total energy needs, and children with MAM receive a food supplement to complement their family diet [14,27]. Most SFP protocols currently provide 500-550kcal/day of ready-to-use supplementary food (RUSF). Similarly, recently published studies indicate that admitting children with a MUAC <125mm leaves very few high risk children untreated [20,21,55].

The combined protocol developed through this study provides a novel MUAC-based protocol to test in operational and clinical trials. The combined protocol was recently tested in a cluster-randomized controlled trial in Kenya and South Sudan, with results of the trial expected in early 2020 [43].

Other research

These results are consistent with and bolster other global child malnutrition studies [23,56]. There is increasing evidence that MUAC-based admission and discharge criteria are effective at improving efficiency and care outcomes [20,57,58]. Several extant protocols that provide supplementary foods to families of children with MAM rather than provide all energy needs with therapeutic foods have been found to be successful [18,47].

Answering the questions of whether a single protocol for the management of MAM and SAM will increase cost-effectiveness and access to treatment are among the objectives of the ComPAS stage 2 randomized controlled trial (the results of which currently under review). Since the conclusion of the ComPAS stage 2 trial, several operational studies and additional RCT's have begun evaluating these questions as well [42,59–62]. The premise is that a single protocol will result in increased coverage of MAM cases before these children deteriorate into SAM. MAM treatment is less costly for a number of reasons: less frequent visits (bi-weekly instead of weekly), less RUTF (one sachet per day), and minimal medical treatments. In this way, we hypothesize that the increase in cost by expanding treatment to MAM will be balanced by the reduction in the more costly treatment of SAM. Additionally, an important aspect of the protocol tested in ComPAS Stage 2 is the optimized dosage for SAM children. The optimized dosage provides two sachets of RUTF per day for all children less than 115mm. In the standard protocol currently used in most countries, the dosage of RUTF is based on weight and ranges between two to five sachets per day. Therefore, an additional aspect of cost savings is not just the reduction in SAM cases, but the reduced dosage of RUTF used for SAM. We will need to see this play out in operational studies in multiple countries to assess the practical implications, and that is what the UN and non-governmental organizations (NGOs) are doing now [63].

Future research can expand on these findings by powering samples to estimate energy needs of smaller subgroups of children with acute malnutrition such as those with oedema and older and larger children with SAM. Primary data collection can be used to obtain more precise data regarding age of children for more granular analysis by age. Additionally, growth differences between children with similar MUACs but in TFP versus SFP clinics can be explored.

Conclusion

Using data from several large therapeutic feeding programs, we found MUAC to be a good proxy for proportional weight gain, demonstrating similar growth pattern changes. Using observed growth, we estimated that 1000 kcal of energy per day is sufficient for recovery of children with uncomplicated acute malnutrition. This suggests that a simplified protocol of two RUTF packets per day for children with MUAC 100mm to <115mm and one RUTF packet per day for children with MUAC 115mm to <125mm is an acceptable therapeutic approach to uncomplicated acute malnutrition. Since most children in our sample were young, we can be most confident or our results for children aged <2 years. Further research should focus on needs of older children. In particular, intervention trials are needed for testing this protocol and other approaches.

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4.2 Paper III: Results for Objective 2

Paper III: **Bailey J,** Opondo C, Lelijveld N, Marron B, Onyo P, Musyoki EN, Adongo SW, Manary M, Briend A, Kerac M. A simplified, combined protocol versus standard treatment for acute malnutrition in children 6-59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan. PLoS Med. 2020;17(7):e1003192. **https://doi.org/10.1371/journal.pmed.1003192**.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	173611	**Title**	Ms.
First Name(s)	Jeanette		
Surname/Family Name	Bailey		
Thesis Title	Simplified, combined protocol for acute malnutrition in children 6-59 months: the ComPAS randomized controlled trial		
Primary Supervisor	Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS Medicine: Bailey J, Opondo C, Lelijveld N, Marron B, Onyo P, Musyoki EN, Adongo SW, Manary M, Briend A, Kerac M. A simplified, combined protocol versus standard treatment for acute malnutrition in children 6-59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan. PLoS Med. 2020;17(7):e1003192. https://doi.org/10.1371/journal.pmed.1003192.		
When was the work published?	July 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This paper describes the primary and secondary outcomes of the ComPAS randomized controlled trial. In this stage of the research, I came up with the idea for the trial, formulated the research questions, obtained funding, wrote the study protocol, managed all trial activities as the principal investigator and project director, cleaned and organized the dataset, conducted the analyses (other than the cost analyses, which are described below), wrote the first draft, managed inputs from co-authors and revised subsequent drafts, responded to peer reviewer comments and finalized the paper for publication in PLOS Medicine. For the cost-effectiveness analysis embedded within the RCT, I conceived the idea for a cost-effectiveness study, sought support from health economists to design the methods, and supported the design of data collection tools. Dr. Lelijveld led the data collection and analyses of the cost results presented in tables 4 and 5. I reviewed and revised the cost results and supported the interpretation of conclusions. Additionally, Dr. Opondo developed the visualization for Figure 2.

SECTION E

Student Signature	Jeanette Bailey
Date	1 April 2021

Supervisor Signature	Dr Marko Kerac
Date	15th April 2021

PLOS MEDICINE

RESEARCH ARTICLE

A simplified, combined protocol versus standard treatment for acute malnutrition in children 6–59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan

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Data Availability Statement: Underlying data, code and supporting documentation for this paper

Abstract

Background

Malnutrition underlies 3 million child deaths worldwide. Current treatments differentiate severe acute malnutrition (SAM) from moderate acute malnutrition (MAM) with different products and programs. This differentiation is complex and costly. The Combined Protocol for Acute Malnutrition Study (ComPAS) assessed the effectiveness of a simplified, unified SAM/MAM protocol for children aged 6–59 months. Eliminating the need for separate products and protocols could improve the impact of programs by treating children more easily and cost-effectively, reaching more children globally.

Methods and findings

A cluster-randomized non-inferiority trial compared a combined protocol against standard care in Kenya and South Sudan. Randomization was stratified by country. Combined protocol clinics treated children using 2 sachets of ready-to-use therapeutic food (RUTF) per day for those with mid-upper arm circumference (MUAC) < 11.5 cm and/or edema, and 1 sachet of RUTF per day for those with MUAC 11.5 to <12.5 cm. Standard care clinics treated SAM with weight-based RUTF rations, and MAM with ready-to-use supplementary food (RUSF). The primary outcome was nutritional recovery. Secondary outcomes included cost-effectiveness, coverage, defaulting, death, length of stay, and average daily weight and MUAC

are available at https://datacompass.lshtm.ac.uk/1151/. The full dataset cannot be made open access due to the presence of participant identifiable content. However, a redacted version will be provided to interested parties, subject to the completion of a request form (available via the repository link above) and signing of a Data Transfer Agreement.

Funding: This study was funded by the United States Agency for International Development Office of U.S. Foreign Disaster Assistance (https://www.usaid.gov/who-we-are/organization/bureaus/bureau-democracy-conflict-and-humanitarian-assistance/office-us), grant number AID-OFDA-G-14-00208 awarded to the International Rescue Committee, and the Children's Investment Fund Foundation (https://ciff.org/) grant reference title 'Reinventing community management of acute malnutrition' awarded to Action Against Hunger. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: ComPAS, Combined Protocol for Acute Malnutrition Study; MAM, moderate acute malnutrition; MUAC, mid-upper arm circumference; NGO, nongovernmental organization; OTP, outpatient therapeutic program; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; SDG, Sustainable Development Goal; SFP, supplementary feeding program; SQUEAC, Semi-Quantitative Evaluation of Access and Coverage; WHZ, weight-for-height *z*-score.

gains. Main analyses were per-protocol, with intention-to-treat analyses also conducted. The non-inferiority margin was 10%. From 8 May 2017 to 31 March 2018, 2,071 children were enrolled in 12 combined protocol clinics (mean age 17.4 months, 41% male), and 2,039 in 12 standard care clinics (mean age 16.7 months, 41% male). In total, 1,286 (62.1%) and 1,202 (59.0%), respectively, completed treatment; 981 (76.3%) on the combined protocol and 884 (73.5%) on the standard protocol recovered, yielding a risk difference of 0.03 (95% CI −0.05 to 0.10, $p = 0.52$; per-protocol analysis, adjusted for country, age, and sex). The amount of ready-to-use food (RUTF or RUSF) required for a child with SAM to reach full recovery was less in the combined protocol (122 versus 193 sachets), and the combined protocol cost US$123 less per child recovered (US$918 versus US$1,041). There were 23 (1.8%) deaths in the combined protocol arm and 21 (1.8%) deaths in the standard protocol arm (adjusted risk difference 95% CI −0.01 to 0.01, $p = 0.87$). There was no evidence of a difference between the protocols for any of the other secondary outcomes. Study limitations included contextual factors leading to defaulting, a combined multi-country power estimate, and operational constraints.

Conclusions

Combined treatment for SAM and MAM is non-inferior to standard care. Further research should focus on operational implications, cost-effectiveness, and context (Asia versus Africa; emergency versus food-secure settings). This trial is complete and registered at ISRCTN (ISRCTN30393230).

Trial registration

The trial is registered at ISRCTN, trial number ISRCTN30393230.

Author summary

Why was this study done?

- For decades, children with severe and moderate acute malnutrition have been treated separately, using different feeding products, protocols, and programs.
- Low coverage limits the global impact of acute malnutrition treatment programs.
- To improve impact and efficiency, we designed a simplified and combined approach to treat acute malnutrition, using mid-upper arm circumference to determine therapeutic food dosage.
- We hypothesized that this new approach would be as effective but more cost-effective than standard care, thereby raising the potential for improved future treatment availability.

What did the researchers do and find?

- We conducted a cluster-randomized trial in Kenya and South Sudan to assess whether recovery in a simplified, combined protocol was non-inferior to standard treatment. Our main secondary objective was to assess cost-effectiveness.
- The needed sample size was calculated for a per-protocol analysis, with a target of 12 clusters of 100 children in each arm (2,400 children in total).
- Recovery in the combined protocol arm was non-inferior to that in the standard protocol arm, with 76.3% recovering in the combined protocol arm and 73.5% recovering in the standard protocol arm (risk difference of 0.03, 95% CI −0.05 to 0.10, $p = 0.52$).
- The average amount of ready-to-use food required for a child with severe malnutrition to reach full recovery was less in the combined protocol arm than in the standard protocol arm (122 versus 193 sachets), and the combined protocol was US$123 less per child recovered (US$918 versus US$1,041).

What do these findings mean?

- A simplified protocol for severe and moderate acute malnutrition is as effective as standard treatment, achieving the same numbers of children recovered.
- The simplified, combined protocol saves money. Resource-constrained health systems could treat more children for the same investment, thereby extending coverage and improving public health impact.
- Prolonged and severe emergencies like the COVID-19 pandemic may increase global food insecurity and malnutrition and strain health systems further, increasing the need for simple, easy-to-use, and cost-effective malnutrition treatment approaches that reduce the strain on health workers and optimize health system resources.

Introduction

Malnutrition is a major global public health problem, contributing to the deaths of approximately 3 million children under age 5 years each year [1]. Acute malnutrition affects more than 50 million children under age 5 and is particularly serious: As well as having a high short-term case fatality rate, it also has important long-term sequelae [2–5]. Tackling malnutrition is unfinished business from the Millennium Development Goals and remains prominent in the Sustainable Development Goals (SDGs). SDG 2.2 aims to "end all forms of malnutrition, including achieving by 2025 the internationally agreed targets on stunting and wasting in children under 5 years of age" [6]. Despite its importance, there is increasing concern that current approaches to acute malnutrition are suboptimal [7–9]. Successful treatments are available, but treatment program coverage is low, with at least 75% of acutely malnourished children 6–59 months old not accessing care [10,11]. This makes achieving impact at national and international levels difficult.

Acute malnutrition can be seen as a continuum condition, but current treatments for acute malnutrition are separated into 2 components: those treating severe acute malnutrition (SAM)

and those treating moderate acute malnutrition (MAM). Children with SAM have the highest risks for morbidity and mortality, but children with MAM remain at risk for adverse outcomes including illness and death [1,12–16]. SAM is currently defined as weight-for-height < −3 standard deviations (*z*-scores) below the WHO reference median and/or a mid-upper arm circumference (MUAC) < 11.5 cm and/or edema; MAM is currently defined as weight-for-height from −3 to <−2 standard deviations (*z*-scores) below the WHO reference median and/or a MUAC from 11.5 cm to <12.5 cm.

SAM and MAM are managed in separate programs, using different food products and protocols. There is currently no globally accepted guidance for the treatment of MAM, and MAM is not always routinely treated [17,18]. International mandate adds an additional layer of complexity: UNICEF supports the treatment of SAM and provides ready-to-use therapeutic food (RUTF) for use in outpatient therapeutic programs (OTPs); the World Food Programme supports the treatment of MAM and provides ready-to-use supplementary food (RUSF) or fortified blended flours for use in supplementary feeding programs (SFPs) [19,20]. In humanitarian settings, providing treatment for both SAM and MAM adds to the logistical and financial burden of health systems. When resources are scarce, and in the many settings where prevalence is not high enough to reach emergency thresholds, treatment of SAM is often prioritized, and children with MAM may not be eligible to receive care unless they deteriorate.

The Combined Protocol for Acute Malnutrition Study (ComPAS) unified the treatment of uncomplicated SAM and MAM for children 6–59 months into one protocol, with simplified diagnostic criteria and a single therapeutic food product. This is the first randomized controlled trial we are aware of to test a simple, MUAC-based dosage protocol for the treatment of SAM and MAM in children 6–59 months. A clinical trial assessing the effectiveness of an integrated SAM/MAM approach using a weight-based dosage protocol found similar recovery and lower therapeutic food costs in the integrated treatment arm [21]. An operational study of children admitted with a MUAC < 12.5 cm and/or edema and treated with a gradually reduced dosage of RUTF based on a combination of MUAC status and weight also found a high overall recovery rate [22]. Multiple studies assessing the use of MUAC in nutrition programs have shown that MUAC is effective at identifying children most at risk of mortality and is simpler and easier to use than weight-for-height measures [23,24]. MUAC gain can be used as a proxy for weight gain [25–28], and rate of weight and MUAC gain in response to treatment appears to decline as children recover [25,26,28,29]. Current standard of care provides a weight-based dosage of up to 200 kcal/kg/day for all children with SAM (S1 Table), but this dosage is based on the rate of weight gain in inpatient settings, which is higher than in outpatient settings [29]. Several recent studies of children with SAM in outpatient settings indicate that recovery with a reduced dosage is similar to recovery with standard treatment [21,22,30,31]. A study of children treated for SAM in Myanmar reduced the dosage to 500 kcal/day of RUTF once children reached a MUAC of 11.0 cm and a weight-for-height *z*-score (WHZ) ≥ −3 and achieved recovery above Sphere standards [30]. A study in Burkina Faso found that a reduced dosage of RUTF offered to SAM patients beginning in the third week of treatment resulted in non-inferior weight gain velocity and similar recovery and length of stay, though height gain velocity was reduced [31]. As children recover from SAM to MAM, current global practice reduces the dosage of energy received to provide a supplement rather than a replacement for the family diet, typically offering 1 sachet of RUSF per day (500–550 kcal/day) [18,32]. We previously conducted a secondary analysis of program data from 5 countries and found that children recovering from acute malnutrition with a MUAC < 12.5 cm may require 1,000 kcal per day, a reduced dosage compared to standard care [25]. The rationale for a reduced dosage is to facilitate increased coverage—and in turn increased public health impact—of treatment in a resource-constrained environment. The optimal dosage achieves the right

balance between meeting individual energy needs and extending treatment to more children. This study contributes to the evidence on the impact of different dosage regimes.

This study aimed to test the hypothesis that the combined protocol would be non-inferior to the standard protocol in terms of recovery, and improve cost-effectiveness.

Methods

Study design

ComPAS was a cluster-randomized non-inferiority trial conducted in 24 health facilities in Nairobi, Kenya, and Aweil East, South Sudan. We selected a cluster-randomized design in order to ensure fidelity to the assigned protocol at the health facility level, and to improve disaggregation of cost data by protocol type. We tested for non-inferiority, assuming recovery under the simplified protocol would be at least as good as under standard care. The clinical trial described in this paper builds on analysis conducted by our team to develop a simplified, combined protocol [25]. We previously published a full description of the protocol for this trial, as well as the methods for the cost-effectiveness analyses [33,34]. Ethical approval was given by the London School of Hygiene & Tropical Medicine (reference 11826), the Kenya Medical Research Institute (reference non-KEMRI 551), and the Ministry of Health in South Sudan (approved 21 November 2016).

Participants

Aweil East, South Sudan, is a rural, agro-pastoralist region in Northern Bahr el Ghazal State with a total population of 309,921 and an under 5 population of 59,574 [35]. Nairobi, Kenya, is an urban area with a total population of 3,078,108 and an under 5 population of 462,849 [36]. Three sub-counties of Nairobi were included in the study: Embakasi North, Embakasi East, and Embakasi West.

Health facilities were eligible for selection as clusters. Only 12 health facilities were operating nongovernmental organization (NGO)–supported nutrition services in Aweil East at the time of randomization, and all were selected for participation. In Nairobi, the Ministry of Health aided selection of 12 health facilities in 3 sub-counties with the highest burden of malnutrition. Of the 32 health facilities in the 3 sub-counties of Nairobi, clinics were selected based on the following factors: the level of care provided (hospitals and dispensaries excluded), the type of care provided (routine child health services available), the population served (slum or peri-urban communities), and expected caseload of malnutrition. Children aged 6–59 months presenting to any of the 24 clinics involved in the study were eligible to enroll (S2 Table). Active case finding was also conducted by community health workers using MUAC to find and refer children. Active case finding was conducted in the same way for all clinics across both treatment arms and countries. Children admitted with a MUAC < 12.5 cm and/or edema (+/++, i.e., mild or moderate) were eligible for inclusion. Children exhibiting signs of a severe illness or danger sign according to the Integrated Management of Childhood Illness (IMCI) algorithm, or not passing the appetite test (consumption of 30 g of RUTF within 20 minutes), were excluded and referred for further assessment and care at an inpatient stabilization center or hospital [33,37].

Clinic-level and individual consent were obtained. Local health authorities and clinic managers gave written permission for their clinics to be included prior to randomization. For individual caretakers of malnourished children, participation was first explained in their local language (Dinka in South Sudan; Kiswahili or English in Nairobi). Caretakers were provided with an information sheet describing details of the interventions, and staff emphasized that treatment would be available to all regardless of whether they chose to participate. A consent

document was signed by caretakers, or by a witness who could attest to the caretaker's verbal consent.

Randomization and blinding

The 24 health clinics were indexed and sent to the senior statistician (CO) based in London, who did not have any prior knowledge of their identities or characteristics. The statistician generated a randomized sequence list stratified by country using the Sealed Envelope randomized sequence generator and applied it to the list of the health facilities [38]. Participants were enrolled in the study arm of the clinic they presented to, by the research officer based at each clinic. Given that the intervention was applied at the facility level, clinic staff could not be blinded to group allocation, and neither could participants. To ensure objective trial management, the principal investigator (JB) was blinded to clinic allocation and outcomes by treatment arm until the last participant exited the trial and the database was locked. For data monitoring purposes during the trial, a data manager sent de-identified data to the PI, with site codes replacing clinic names and all information identifying clinics or treatment arms removed. The senior statistician revealed clinic allocation only after the trial database had been closed [33].

Study procedures

In standard protocol clinics, children with SAM received RUTF according to weight (200 kcal/kg/day) in the OTP (S2 Table). Children with MAM received 500 kcal/day of RUSF (1 sachet/day) in the SFP. The OTPs and SFPs in the control arm in both countries operated from the same clinics with the same staff. In combined protocol clinics, children with a MUAC < 11.5 cm and/or edema (+/++) received 1,000 kcal RUTF/day (2 sachets/day), and children with a MUAC of 11.5 to <12.5 cm and no edema received 500 kcal RUTF/day (1 sachet/day). When children met the criteria for transition from SAM to MAM (MUAC ≥ 11.5 cm and no edema for 2 consecutive visits), they were switched from 2 sachets of RUTF/day to 1 sachet of RUTF/day. This reduction in dosage is based on the slowing rate of growth that we observed at a MUAC of approximately 11.5 cm in our stage 1 study [25] and aligns with UN guidance on the treatment of MAM [18,32]. Children in the combined protocol arm were registered as either an OTP or SFP patient based on their admission MUAC.

In the standard protocol, children were only included in this analysis if their MUAC on admission was <12.5 cm and/or they had edema (+/++). If they also met the WHZ < −2 criterion on admission and reached WHZ ≥ −2 prior to reaching MUAC≥ 12.5 cm during treatment, they were not discharged until they had a MUAC measurement of ≥12.5 cm for 2 consecutive visits, to ensure parity of the definition of recovery between the intervention and control arms.

In both arms, children with SAM came once a week for a medical and nutritional evaluation and received systematic medications per the national protocol. Children with MAM attended every 2 weeks and received only a nutritional consultation, unless they required medical attention. Children who were found not to be gaining adequate weight or not progressing towards recovery (non-responders) were referred for medical assessment and/or inpatient care. Defaulters were traced by community health workers and referred to care if they were found to still be malnourished (though they were not re-enrolled in the study). All non-nutritional components of treatment such as systematic medications, frequency of follow-up, and home visits to prevent defaulting were identical between the combined and standard protocol arms. Full details of the combined and standard protocols were previously published [33] and are summarized in S2 Table.

Outcomes

The primary outcome was recovery in the per-protocol analysis, defined as reaching a MUAC measurement of ≥12.5 cm and no edema for 2 consecutive visits (weekly for SAM and biweekly for MAM). Secondary outcomes included cost-effectiveness, death (including post-defaulting deaths confirmed during defaulter tracing and follow-up phone calls when possible), non-response (16 weeks in treatment without achieving recovery), transfer (to either a stabilization center or a different facility), and defaulting (3 consecutive missed visits). The outcome categories recovery, death, non-response, defaulting, and transfer were mutually exclusive. To account for MAM children attending visits biweekly, we extended the non-response cutoff for all children to 17 weeks to evaluate the status of MAM children who would not have come for a visit at 16 weeks. Clinic staff determined whether children had met specified criteria in the protocol and discharged them from further follow-up. The criteria for each outcome (e.g., recovery being defined by 2 consecutive visits with a MUAC ≥ 12.5 cm and no edema) were prespecified in the study protocol, and outcomes were assigned according to the strict definitions described in the study protocol. This process ensured that any discharge errors by clinic staff would be identified and accounted for during the analysis. An additional outcome category of early discharge was added during the analysis phase to account for children mistakenly discharged by the clinic staff before their outcome could be ascertained. The providers in each of the clinics were given on-site practical trainings in anthropometry and refresher trainings. Details of the procedures for taking anthropometric measurements are available in S1 Text. Research officers (registered nutritionists and supervisors for clinic staff) oversaw and repeated measurements to ensure agreement with clinic staff. Analyses of length of stay, average daily weight gain (g/kg/day), and average daily MUAC gain (mm/day) were conducted on children who achieved recovery. All outcomes were measured at the individual level. A formal data and safety monitoring board was not planned due to the expected short duration of recruitment. Instead, a trial safety committee comprising an independent chair and a statistician conducted a safety review at the midpoint of the trial. Outcomes and adverse events, including hospitalizations and deaths, were reported to the safety committee at the midpoint of recruitment. The committee, upon reviewing the safety report, recommended continuation of recruitment with no amendments to the protocol [33].

To assess cost-effectiveness, we calculated costs from a societal perspective, using accounting data, interviews with key informants, and survey questionnaires given to a subset of staff and all caregivers. Details have been described in our cost analysis methods paper [34]. We categorized costs into treatment, outreach, supply logistics, supervision, management, and household costs for each country.

We used a modified version of the Semi-Quantitative Evaluation of Access and Coverage (SQUEAC) assessment to assess coverage [39]. The SQUEAC method uses Bayesian techniques with a small sample survey to produce single coverage estimates. The coverage surveys assessed only MUAC and edema, in keeping with the study definitions of SAM and MAM. Coverage estimates are presented for SAM (MUAC < 11.5 and/or edema) and MAM (MUAC 11.5 to <12.5 cm) in each country and for each arm.

Statistical analysis

Our sample size was designed to detect non-inferiority of recovery for the combined protocol compared to the standard protocol in the per-protocol analysis with a 10% non-inferiority margin and 80% power at a 2-sided level of significance of 5%. Based on these parameters, 12 clusters per arm were required, with 100 children in each cluster. The 10% non-inferiority margin was selected based on previous program data reporting a recovery rate of 85%, with a

minimum acceptable recovery rate of 75% per Sphere standards [40]. An intra-cluster correlation coefficient of 0.05 was assumed, based on results of a similar trial [21]. An additional adjustment to the sample size calculation was made to anticipate losses to follow-up and crossovers (children who are cross-registered across arms and need to be excluded during the analysis), in order to determine how many children should be recruited per cluster to ensure 100 children with completed treatment for the per-protocol analysis. Thus, the sample size was calculated to recruit enough children per cluster so that when defaulters (and other non-adherents, such as transfers or early discharges) were removed from the denominator, the power of the study would be maintained. Losses to follow-up were expected to be 15%, based on Sphere standards, and crossovers were expected to be 5%, so we aimed to recruit 150 children per cluster to achieve our target of 100 per cluster for the per-protocol analysis [33,41,42].

We used CommCare for data management [43]. In Kenya, clinic-based research officers entered data on Samsung Galaxy Tab A tablets running Android OS v.5.1.1 and uploaded data to the CommCare server. In South Sudan, nutrition supervisors initially collected data on paper forms. Data were then entered by 2 data entry clerks into Samsung Galaxy Tab A tablets running Android OS v.4.4 and uploaded to the CommCare server. Data entry onto paper forms and tablets was supervised and cross-checked by field coordinators. Data entry errors were logged and checked by the field coordinators and the principal investigator before incorporation into the database [33].

We conducted both per-protocol and intention-to-treat analyses. We designed this trial with per-protocol as the main analysis because it is more conservative and is the recommended approach for primary analysis of non-inferiority trials [33,44,45]. Non-inferiority was assessed only for the primary outcome of recovery. For secondary outcomes we explored evidence of a difference, rather than non-inferiority. The intention-to-treat analysis included all children enrolled, and the per-protocol analysis excluded children who did not complete treatment: those who exited the study as transfers to other facilities, defaulters lost to follow-up, or early discharges from treatment. Non-inferiority of the primary outcome of recovery was defined as a difference in proportion of children recovering from acute malnutrition with the upper bound of the 95% confidence interval being less than 10%. We used binomial regression models for binary outcomes and linear regression models for continuous outcomes. In both approaches we used clustered robust standard errors to adjust for repeated measures (clustering) within health facilities. We adjusted for the baseline characteristics of age, sex, and country in all the adjusted analyses. For costs with the greatest uncertainty we conducted a univariate sensitivity analysis. We present a mean base-case value across both countries, in US dollars, for cost per child treated, cost per child recovered, and the incremental cost of implementing the combined protocol compared to standard treatment. Analysis was conducted using Stata/IC v.13.1 [46]. Stata's zscore06 package was used to calculate WHZ, height-for-age *z*-score, and weight-for-age *z*-score (according to WHO Child Growth Standards) and flags [47].

The trial is registered at ISRCTN: trial number ISRCTN30393230 (http://www.isrctn.com/ISRCTN30393230). This study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (S3 Text; S4 Text).

Results

Recruitment began 8 May 2017 and ended 31 March 2018. Trial activities were completed in Kenya on 31 July 2018 and in South Sudan on 31 August 2018, when the last enrolled children completed treatment. Among the children attending nutrition services at the participating health clinics, 157 children had WHZ < -2 but did not meet eligibility criteria because they

had a MUAC ≥ 12.5 cm and no edema; these children were enrolled in a sub-study and their outcomes will be presented in a forthcoming paper. A total of 4,110 children met eligibility criteria and were enrolled (Fig 1). Of these, 30 were excluded from analysis due to a missing admission date. Two more were excluded due to implausible MUAC values. The intention-to-treat analysis included 24 clusters and 4,078 children. After removing those who did not complete treatment, the per-protocol analysis included 24 clusters and 2,488 children (Fig 1). The target per-protocol sample size of 100 children per cluster was met: In the combined protocol arm the median sample per cluster was 107.5 (IQR 99.5–118); in the standard protocol arm the median sample per cluster was 102.4 (IQR 97–107.5).

Baseline characteristics were similar in the 2 study arms (Table 1). There were more females than males in the sample, and children had a mean age of around 17 months. About three-quarters of the children were aged between 6 and 24 months. Baseline characteristics by country are shown in S3 Table. Inter-country differences include the following: children in South Sudan were on average older than in Kenya (mean 22 versus 12 months); the Sudanese population was more rural, with household income mainly from fishing and farming; the Kenyan setting was more urban, with most household income from shopkeeping, casual labor, and salaried work; maternal education level in South Sudan was low, whereas most mothers in Kenya reported secondary level education (S3 Table).

In the per-protocol analysis, children in the combined protocol arm had non-inferior recovery (76.3% in the combined arm versus 73.5% in the standard arm; adjusted risk difference 0.03, 95% CI −0.05 to 0.10, $p = 0.52$) (Table 2; Fig 2). There was no evidence of a difference in the secondary outcomes death (1.8% versus 1.8%; adjusted risk difference 0.00, 95% CI −0.01 to 0.01, $p = 0.87$) and non-response (21.9% versus 24.7%; adjusted risk difference −0.03, 95% CI −0.10 to 0.05, $p = 0.48$). Results in the intention-to-treat analysis were similar, with non-inferior recovery in the combined protocol (47.6% in the combined arm versus 43.8% in the standard arm; adjusted risk difference 0.03, 95% CI −0.06 to 0.13, $p = 0.47$) (Table 2; Fig 2). There was no evidence of a difference between arms in the risk of the secondary outcomes death (1.1% versus 1.0%; adjusted risk difference 0.00, 95% CI −0.01 to 0.01, $p = 0.79$), non-response (13.7% versus 14.7%; adjusted risk difference −0.01, 95% CI −0.05 to 0.04, $p = 0.73$); defaulting (24.7% versus 30.7%; adjusted risk difference −0.06, 95% CI −0.15 to 0.03, $p = 0.20$), and transfer to inpatient care (1.7% versus 1.1%; adjusted risk difference 0.01, 95% CI −0.01 to 0.02, $p = 0.42$) (Table 2). The intra-cluster correlation coefficient for recovery was 0.05 (95% CI 0.01 to 0.08) for the per-protocol analysis and 0.06 (95% CI 0.02 to 0.09) for the intention-to-treat analysis.

Among children who recovered, there was no evidence of a difference between the combined and standard protocols in length of stay (65.4 versus 65.0 days; adjusted mean difference −0.55, 95% CI −5.75 to 4.65, $p = 0.83$), average daily weight gain (1.9 versus 1.9 g/kg/day; adjusted mean difference 0.08, 95% CI −0.13 to 0.29, $p = 0.42$), and average daily MUAC gain (0.2 versus 0.2 mm/day; adjusted mean difference −0.01, 95% CI −0.04 to 0.02, $p = 0.45$) (Table 3).

Coverage results were similar for both protocols, with overlapping confidence intervals for all results. In Kenya, the coverage for SAM (MUAC < 11.5 cm and/or edema) was estimated at 54.9% (95% CI 41.2% to 68.0%) and 52.9% (95% CI 39.1% to 66.2%) for the combined and standard protocol arms, respectively. For MAM (MUAC 11.5 to <12.5 cm), coverage was 48.6% (95% CI 38.0% to 59.4%) and 47.3% (95% CI 37.1% to 58.0%) for the combined and standard protocol arms, respectively. In South Sudan, coverage for SAM was estimated at 45.9% (95% CI 32.5% to 59.9%) and 62.5% (95% CI 47.8% to 75%) for the combined and standard protocol arms, respectively. For MAM, coverage was 21.3% (95% CI 14.9% to 29.2%) and 26.3% (95% CI 19.2% to 35.1%) for the combined and standard protocol arms, respectively (S4 Table).

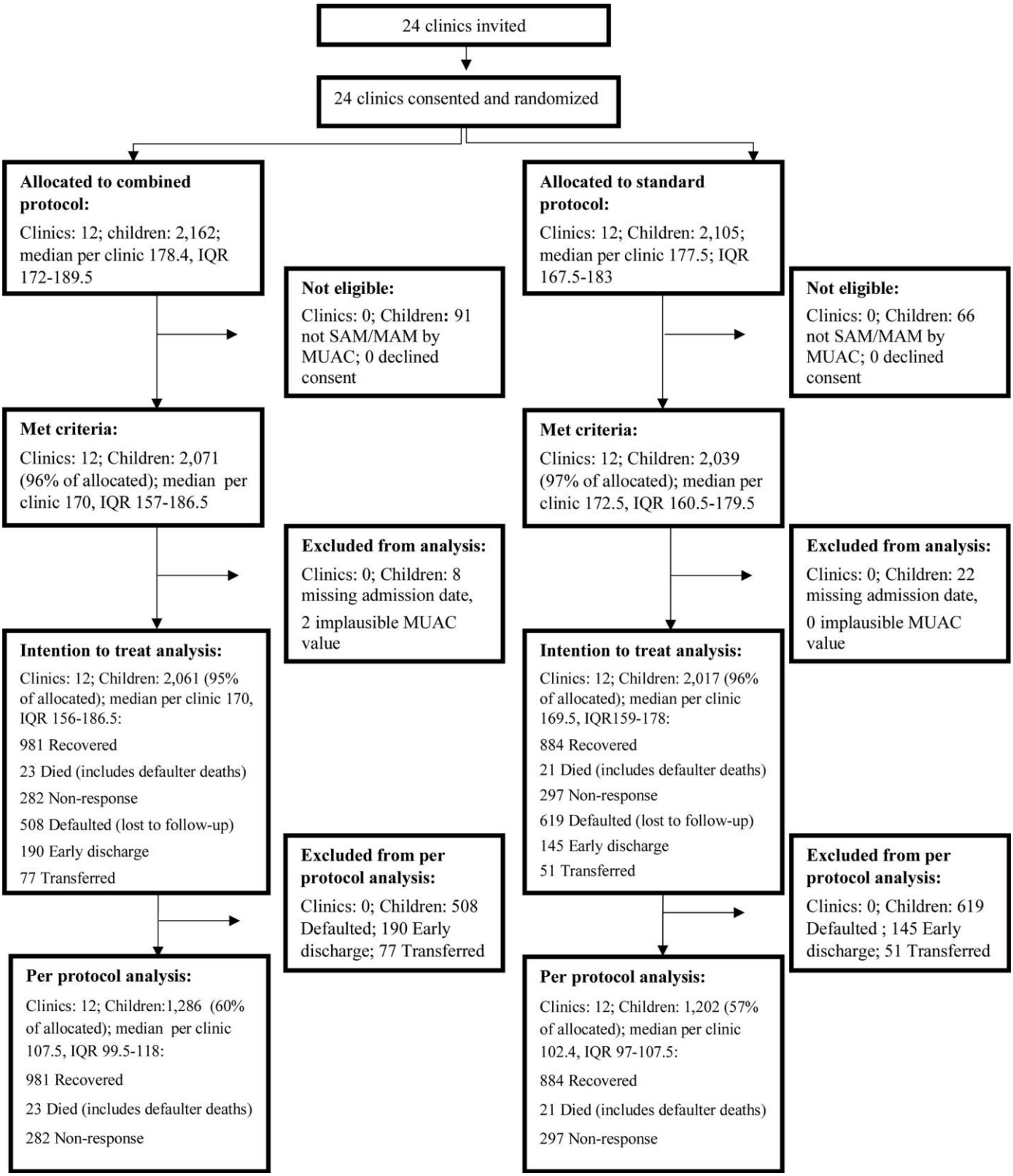

Fig 1. Trial profile. MAM, moderate acute malnutrition; MUAC, mid-upper arm circumference; SAM, severe acute malnutrition.

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Table 1. Admission characteristics of children in the combined and standard protocols.

Characteristic	Combined protocol (*N* = 12, *n* = 2,071)	Standard protocol (*N* = 12, *n* = 2,039)
Sex and age		
Male, *n* (%)	841 (41%)	841 (41%)
Age in months, mean (SD)	17.4 (11.4)	16.7 (10.7)
Age category, *n* (%)		
6 to <24 months	1,502 (73%)	1,542 (76%)
≥24 months	564 (27%)	495 (24%)
Anthropometrics		
Weight (kg), mean (SD)	7.2 (1.6)	7.3 (1.6)
Height (cm)[a], mean (SD)	72.9 (8.9)	73.0 (8.7)
MUAC (cm), mean (SD)	11.7 (.55)	11.7 (.59)
WHZ, mean (SD)	−2.5 (1.0)	−2.3 (3.4)
HAZ, mean (SD)	−2.1 (1.6)	−1.9 (1.6)
WAZ, mean (SD)	−2.9 (1.0)	−2.7 (1.1)
MUAC < 11.5 cm, *n* (%)	601 (29%)	634 (31%)
WHZ < −3	352 (59%)	346 (55%)
WHZ ≥ −3 to <−2	189 (32%)	208 (33%)
WHZ ≥ −2	60 (10.0%)	80 (12.6%)
MUAC 11.5 to <12.5 cm, *n* (%)	1,461 (71%)	1,397 (69%)
WHZ < −3	258 (18%)	158 (11%)
WHZ ≥ −3 to <−2	650 (45%)	550 (39%)
WHZ ≥ −2	553 (38%)	689 (49%)
Edema (+ or ++), *n* (%)	23 (1%)	24 (1%)
Other participant characteristics		
Child breastfed in last 24 hours, *n* (%)	1,437 (69%)	1,426 (70%)
Caretaker reports any morbidity[b] in child in past week, *n* (%)	1,320 (64%)	1,179 (58%)
Fever	787 (38%)	714 (35%)
Diarrhea	521 (25%)	517 (25%)
Cough	651 (31%)	694 (34%)
Health care sought in prior week	489 (24%)	339 (20%)
HIV status, *n* (%)		
Positive	9 (0%)	5 (0%)
Exposed (mother)	19 (1%)	17 (1%)
Disabled (physically or mentally)	44 (2%)	38 (2%)
Tuberculosis (+), *n* (%)	6 (0%)	3 (0%)
Household characteristics		
Mother is caretaker, *n* (%)	1,978 (96%)	1,923 (94%)
Maternal educational achievement, *n* (%)		
None	927 (47%)	837 (44%)
Pre-primary	9 (1%)	13 (1%)
Primary	475 (24%)	485 (25%)
Secondary	566 (29%)	585 (30%)
College tertiary	0 (0%)	1 (0%)
Number of children under 5 years in the home, mean (SD)	1.5 (1.0)	1.7 (0.8)
Access to toilet, *n* (%)	1,314 (64%)	1,342 (66%)
Water source, *n* (%)		

(*Continued*)

Table 1. (Continued)

Characteristic	Combined protocol (*N* = 12, *n* = 2,071)	Standard protocol (*N* = 12, *n* = 2,039)
Household tap	92 (4%)	174 (9%)
Community tap/tap stand	684 (33%)	742 (36%)
Hand pump/borehole	746 (36%)	518 (25%)
Borehole (private)	162 (8%)	452 (22%)
Vendors	227 (11%)	77 (4%)
Open water	152 (7%)	67 (3%)
Livelihood/main source of income, *n* (%)		
No income	10 (1%)	112 (6%)
Sale of items (grass, firewood, livestock)	324 (16%)	97 (5%)
Fishing/farming	649 (31%)	559 (27%)
Business/shopkeeper	226 (11%)	586 (29%)
Casual labor	529 (26%)	586 (29%)
Salaried work	301 (15%)	284 (14%)
Other	21 (1%)	29 (1%)
Ever no food to eat[c], *n* (%)		
Never	1,022 (49%)	1,294 (64%)
Rarely	550 (27%)	380 (19%)
Sometimes	407 (20%)	309 (15%)
Often	73 (4%)	43 (2%)
Don't know	2 (0%)	7 (0%)
Ever go to sleep without enough food[c], *n* (%)		
Never	1,205 (50%)	1,189 (58%)
Rarely	543 (26%)	490 (24%)
Sometimes	454 (22%)	291 (14%)
Often	39 (2%)	43 (2%)
Don't know	2 (0%)	20 (1%)
Any household member go whole day without eating anything[c], *n* (%)		
Never	1,097 (53%)	1,238 (61%)
Rarely	507 (25%)	438 (22%)
Sometimes	421 (20%)	279 (14%)
Often	37 (2%)	43 (2%)
Don't know	1 (0%)	35 (2%)

N = number of clusters; *n* = individual children eligible for treatment.

[a]Recumbent length was taken for children 6–23 months, and standing height was taken for children 24 months and older.

[b]"Any morbidity" includes diarrhea, fever, cough, vomiting, skin infection, and other illness.

[c]From Household Hunger Scale.

HAZ, height-for-age *z*-score; MUAC, mid-upper arm circumference; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

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Kaplan–Meier plots showing the time to recovery are presented in S1–S6 Figs. Median time to recovery in the per-protocol analysis was approximately 10 weeks, with similar time to recovery in both arms.

Data from research grant accounts, NGO operational accounts, 83 key informant interviews, and 64 caregiver interviews were used to compute the total economic costs per

Table 2. Primary and secondary outcomes (per-protocol and intention-to-treat analyses).

Outcome	Standard protocol		Combined protocol		Unadjusted		Adjusted	
	n	Percent	*n*	Percent	Risk difference[§] (95% CI)	*p*-Value	Risk difference[§] (95% CI)	*p*-Value
Per-protocol[a]								
Primary outcome								
Recovery	884	73.5%	981	76.3%	0.03 (−0.06 to 0.11)	0.52	0.03 (−0.05 −0.10)	0.52
Secondary outcomes								
Death	21	1.8%	23	1.8%	0.00 (−0.01 to 0.01)	0.95	0.00 (−0.01 to 0.01)	0.87
Non-response	297	24.7%	282	21.9%	−0.03 (−0.11 to 0.05)	0.49	−0.03 (−0.10 to 0.05)	0.48
Intention-to-treat[b]								
Primary outcome								
Recovery	884	43.8%	981	47.6%	0.04 (−0.06 to 0.14)	0.46	0.03 (−0.06 to 0.13)	0.47
Secondary outcomes								
Death	21	1.0%	23	1.1%	0.00 (−0.01 to 0.01)	0.84	0.00 (−0.01 to 0.01)	0.79
Non-response	297	14.7%	282	13.7%	−0.01 (−0.06 to 0.04)	0.66	−0.01 (−0.05 to 0.04)	0.73
Defaulting	619	30.7%	508	24.7%	−0.06 (−0.15 to 0.03)	0.20	−0.06 (−0.15 to 0.03)	0.20
Transfer	51	2.5%	77	3.7%	0.01 (−0.01 to 0.04)	0.38	0.01 (−0.01 to 0.03)	0.17
Inpatient	23	1.1%	35	1.7%	0.01 (−0.01 to 0.02)	0.51	0.01 (−0.01 to 0.02)	0.42
New facility	28	1.4%	42	2.0%	0.01 (−0.01 to 0.02)	0.44	0.01 (−0.01 to 0.02)	0.30
Early discharge	145	7.2%	190	9.2%	0.02 (−0.04 to 0.08)	0.53	0.02 (−0.02 to 0.06)	0.36

Unadjusted: all children with outcome measures, not adjusted for any demographic or study design characteristics. Adjusted: adjusted for age, sex, and country. *N* = number of clusters; *n* = number of children eligible for follow-up.

[§]Standard errors adjusted for clustering within facilities.

[a]Standard protocol: *N* = 12, *n* = 1,202; combined protocol: *N* = 12, *n* = 1,286.

[b]Standard protocol: *N* = 12, *n* = 2,017; combined protocol: *N* = 12, *n* = 2,061.

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treatment arm and country (Table 4). To reach recovery in Kenya, SAM children in the standard protocol arm received on average 148 sachets of ready-to-use food (RUTF and RUSF), and SAM children in the combined protocol arm received on average 105 sachets of RUTF. To reach recovery in South Sudan, SAM children in the standard protocol arm received on average 209 sachets of RUTF and RUSF, and SAM children in the combined protocol arm received on average 133 sachets of RUTF. Overall, the average amount of ready-to-use food required for a child with SAM to reach full recovery (MUAC ≥ 12.5 cm and no edema for 2 consecutive visits) was lower in the combined protocol arm than in the standard protocol arm (122 versus 193 sachets). Combining mean costs and recovery rates across countries, per the statistical power of the study, the combined protocol costs US$123 less per child recovered than the standard protocol (Table 5). The input costs partially include the added costs of running a research trial, as these could not be fully separated from treatment program costs.

Among the 1,127 children who defaulted, 1,103 (97.9%) were followed up with home visits. Of these, only 386 (35.0%) were home at the time of the defaulter tracing visit and had their status verified. Among children traced with status verified, 157 (69.2%) in the standard protocol arm and 83 (52.2%) in the combined protocol arm were found to be still malnourished (with a MUAC < 12.5 cm and/or edema), 63 (27.8%) in the standard protocol arm and 72 (45.3%) in the combined protocol arm had recovered, 6 (2.6%) in the standard protocol arm and 2 (1.3%) in the combined protocol arm had died, and 1 (0.4%) in the standard protocol arm and 2 (1.3%) in the combined protocol arm were unknown. Among children with SAM, 284/641 (44.3%) defaulted in the standard protocol arm, and 209/617 (33.8%) defaulted in the

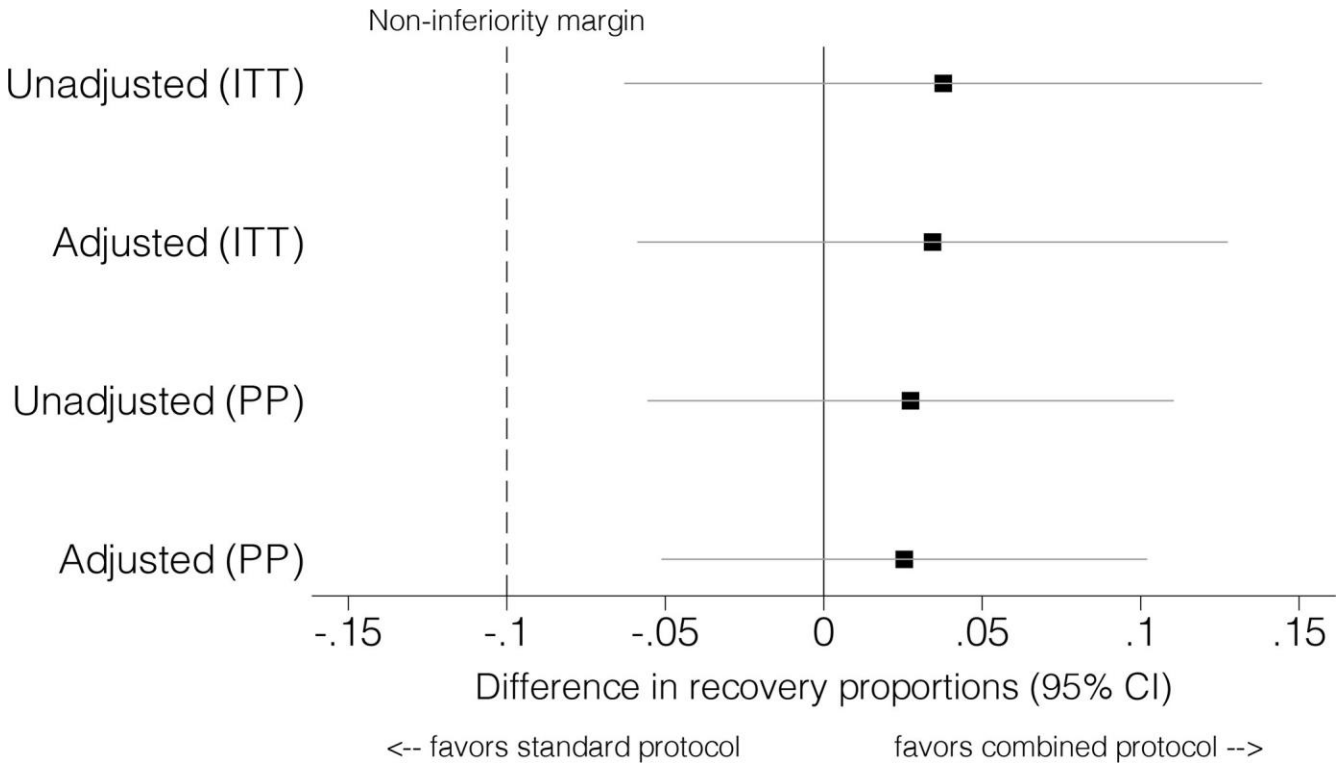

Fig 2. Per-protocol (PP) and intention-to-treat (ITT) analyses of recovery.

https://doi.org/10.1371/journal.pmed.1003192.g002

combined protocol arm. Among children with MAM, 348/1,376 (25.3%) defaulted in the standard protocol arm and 308/1,444 (21.3%) defaulted in the combined protocol arm.

In exploratory analyses of sub-groups, children with SAM, children with MAM, children aged <24 months, children aged ≥24 months, SAM children weighing ≥8 kg, children with a MUAC 11.5 to <12.5 cm but WHZ < −3, children in Kenya, and children in South Sudan recovered similarly under the combined protocol compared to the standard protocol (S5 Table).

Discussion

ComPAS compared a simplified, combined protocol for acute malnutrition to standard care, and found non-inferior nutritional recovery in the combined protocol arm relative to the

Table 3. Secondary outcomes among recovered children.

Outcome	Standard protocol (*N* = 12, *n* = 884)		Combined protocol (*N* = 12, *n* = 981)		Unadjusted		Adjusted	
	Mean	SE	Mean	SE	Mean difference	*p*-Value	Mean difference	*p*-Value
Length of stay (days)	65.0	2.31	65.4	2.24	0.42 (−6.19 to 7.04)	0.90	−0.55 (−5.75 to 4.65)	0.83
Average daily weight gain (g/kg/day)	1.9	0.08	1.9	0.08	0.06 (−0.17 to 0.29)	0.61	0.08 (−0.13 to 0.29)	0.42
Average daily MUAC gain (mm/day)	0.2	0.01	0.2	0.01	−0.01 (−0.05 to 0.02)	0.39	−0.01 (−0.04 to 0.02)	0.45

Unadjusted: all children with outcome measures, not adjusted for any demographic or study design characteristics. Adjusted: adjusted for age, sex, and country. *N* = number of clusters; *n* = number of children eligible for follow-up.
MUAC, mid-upper arm circumference.

https://doi.org/10.1371/journal.pmed.1003192.t003

Table 4. Input costs by country setting and treatment arm.

Cost category	Input costs—South Sudan		Input costs—Kenya	
	Combined protocol	Standard protocol	Combined protocol	Standard protocol
Treatment (includes product)	$237,887	$243,991	$176,251	$174,164
Product only	$34,863	$40,967	$22,897	$20,196
SAM	$15,132	$26,492	$6,576	$6,678
MAM	$19,731	$14,474	$16,321	$13,518
Outreach	$71,329	$71,329	$20,766	$20,766
Supply logistics	$57,640	$69,220	$30,756	$30,756
Supervision	$128,917	$128,917	$14,125	$15,919
Management	$101,346	$101,346	$41,397	$41,397
Household	$8,861	$9,891	$11,563	$11,680
Total	$605,979	$624,692	$294,859	$294,683

All values in US dollars.

MAM, moderate acute malnutrition; SAM, severe acute malnutrition.

https://doi.org/10.1371/journal.pmed.1003192.t004

standard care arm. The findings of the per-protocol and intention-to-treat analyses were similar. Clinical effectiveness was similar, with no evidence of a difference for the secondary outcomes death, non-response, defaulting, transfer to inpatient care, length of stay, program coverage, average daily weight gain, and average daily MUAC gain. Outcomes were similar between the study arms in exploratory analyses of sub-groups, including when disaggregated by SAM or MAM, and by country. The combined protocol cost less per child recovered than the standard protocol, especially for treatment of children with SAM and in the South Sudan context.

This study contributes evidence on integrated SAM/MAM treatment protocols, MUAC-based programming, and novel dosage regimes, which carry certain programmatic benefits: simplicity, ease of use, and potential cost-effectiveness. The combined protocol tested in this trial was the first to our knowledge to use a simple, MUAC-based dosage. Our findings are consistent with previous studies on integrated management of SAM and MAM with novel dosage regimes: a clinical trial in Sierra Leone that used a weight-based dosage protocol, with similar recovery and lower therapeutic food costs in the intervention arm of the study [21], and an operational trial in Burkina Faso that achieved recovery above Sphere standards and used less therapeutic food than standard programs [22].

Table 5. Base-case cost-effectiveness results of the combined versus standard protocol.

Outcome	Combined protocol	Standard protocol
Total cost (US dollars)	$900,838	$919,376
Number of children in program	2,071	2,039
Recovery rate (intention-to-treat)	48%	44%
Number of children recovered	981	884
Cost per child treated (US dollars)	$435	$451
Cost per child recovered (US dollars)	$918	$1,041
Incremental cost (total) (US dollars)	−$18,538	Ref
Incremental cost (per child recovered) (US dollars)	−$123	Ref

ITT, intention-to-treat; USD, US dollars.

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Strengths of this study included comparison against the "gold standard" of standard care: community-based management of acute malnutrition at health clinics offering OTP and SFP in the same physical location, with RUSF offered to children with MAM instead of fortified blended flours. ComPAS was designed this way to capture the value added by simplifying and combining treatment. The reality is that many standard care programs are not able to provide RUSF for children with MAM, or the treatments for SAM and MAM are offered in separate physical locations. Another strength was the inclusion of 2 different contexts contributing to a combined dataset. The multi-country nature of the trial increases the generalizability of the results, with both rural and urban settings contributing data.

ComPAS faced several operational limitations. The contexts in Nairobi and Aweil East are very different, but the study sites were not large enough to be independently powered. Therefore, the analysis is only powered for combined multi-country estimates. Though our inclusion criteria included children up to 59 months, the majority were less than 24 months, so care should be taken in extrapolating the results to older or larger children. A non-inferiority margin of 10% was selected in consideration of previous program data from Aweil East and Nairobi. Actual proportions recovered are within a slimmer margin, with adjusted and unadjusted risk differences for both the per-protocol and intention-to-treat analyses within a 5%–6% margin (Table 2; Fig 2). In Aweil East, access to 4 of the clinics during the rainy season (May to November) was limited. Two of these clinics implemented the combined protocol, and 2 of the clinics implemented the standard protocol. One of the clinics was so inaccessible that supplies could not be delivered for more than 3 months. In Nairobi, mothers were often unable to take time off work to bring their children for regular visits, and some children with medical complications were not admitted to inpatient care for the same reason. The health clinics in Kenya were affected by a national nurse's strike from June to November 2017, which resulted in brief clinic closures and reduced availability of nursing staff. A national presidential election in August 2017, followed by a repeat election in October 2017, contributed to an atmosphere of uncertainty and some instability in the areas of Nairobi where the study took place. Many children were not able to attend their scheduled visits for several weeks during each election period, while families traveled to their rural homes to vote. All the factors above contributed to high defaulting in both contexts, reflected similarly in both arms, and may have negatively affected average daily weight gains. We have no reason to suspect that treatment acceptability had any role in defaulting. High defaulting drove down the overall recovery rates in the intention-to-treat analyses, which did not meet Sphere standards [40]. High defaulting also inflated the cost per child recovered. Defaulting did not impact our assessment of non-inferiority of recovery as the required number of participants completing treatment was met across clusters and arms.

The same underlying factors that drove high defaulting in both arms also contributed to frequent missed visits and longer lengths of stay. We do not attribute the longer lengths of stay to a difference in dosage protocol, as the lengths of stay were similar between arms. Where defaulting and missed visits are common, extending the period in treatment allows for more children to reach recovery. In our analyses, many children went on to recover after the 16-week cutoff for non-response (S1 Fig; S2 Fig).

The cost savings assessed in this trial were limited in scope. Though our method for assessing cost-effectiveness removed many of the research-specific costs [34], it was not possible to fully separate research versus programming costs in the analysis, so the total cost per child is higher than in many program settings. The costs reflect the combined inputs of NGOs and ministries of health, both of which contributed to the treatment of children. Additionally, the settings of Nairobi, Kenya, and Aweil East, South Sudan, have unique cost implications that may not affect other programs, such as the high costs of rent in a capital city and the high

logistics and security costs of operating a clinical trial in a conflict-affected context. Average costs in a non-research setting, although highly variable by context, are often around US$200 per child recovered [48,49].

There were large differences in costs between countries. It is important to note that costing results reflect the caseloads and characteristics of the sample at the country level, but the study is not statistically powered to make conclusions about differences in effectiveness. In South Sudan, there were 3 main reasons for cost savings in the combined protocol: (1) higher recovery and lower length of stay in the combined protocol arm (S5 Table), (2) a higher burden of SAM (with a reduced dosage of RUTF compared to the standard protocol), and (3) an independent supply chain. In Kenya, the larger proportional burden of MAM to SAM cases (S3 Table) and the presence of a centralized medical supply chain through the national government meant cost savings were not apparent. RUTF had a slightly higher price than RUSF (US $0.33 versus US$0.29 per sachet), which affected the cost of MAM treatment in the combined protocol.

Future studies should assess whether additional savings can be achieved from increased efficiencies throughout the larger system for managing acute malnutrition in operational settings. Further research is needed to assess cost-effectiveness in a scaled-up system treating SAM and MAM in 1 protocol with 1 food product across a variety of contexts. Operational studies could assess the impact of a simplified, combined protocol on SAM/MAM caseloads and resource use across multiple years. Potential cost savings may be possible through the prevention of SAM, with its associated medical complications and systematic medications. In the longer term, cost savings from increased efficiency and a reduction in SAM caseload may spread further upstream, addressing more of the MAM caseload. Earlier treatment of acute malnutrition is likely to result in fewer long-term implications, helping children to better survive and thrive.

Adoption of a simplified and combined protocol may simplify operations in resource-constrained settings. A combined protocol reduces the need to procure 2 separate products for SAM and MAM treatment, streamlines program logistics and staff training, and enables a more holistic continuum of care for children with acute malnutrition. A simplified protocol may also facilitate delivery of treatment by community health workers, to improve access and reduce defaulting, an important area of work that calls for research. In contexts where children are highly vulnerable to malnutrition—particularly in crises and chronically fragile situations—a combined protocol may offer some protection, enabling children to benefit from treatment before they deteriorate into life-threatening SAM. The optimal diagnostic criteria and dosage of therapeutic foods may differ by setting, and further research should explore these setting-specific issues and the operational and physiological impacts of expanding treatment of MAM [17]. The potential benefits of a simplified protocol may be weighed against economic considerations including implications for the supply chain of ready-to-use foods, and the impact on caseload and cost when treatment is made more readily available to moderately malnourished children. Further research is also needed to assess the safety and effectiveness of a reduced dosage protocol in children with SAM and in older or larger children. Though our study did not find evidence of harm among any sub-groups, including those with SAM and older children, future studies could be powered to assess those populations specifically. Our findings are consistent with other studies that indicate that a reduced dosage for SAM does not lower recovery [21,22,30,31], but research is needed to understand why a reduced dosage is effective and the contextual factors that affect recovery. Investigating the effects of context (e.g., differences between African and Asian settings, differences between food-insecure settings and food-secure settings, and the impact of seasonality) is a priority.

The reality is the current system fails to reach the majority of children who need treatment, and resources are already limited. If the global health community is to meet SDG nutrition

targets, new approaches are urgently needed. This is particularly true with the emergence of SARS-CoV-2, which has further necessitated a consideration of simplified, easy-to-use, and cost-effective nutrition treatment approaches. The number of malnourished children may rise as a result of the pandemic due to economic and biological factors, and the ability of the health system to respond may be strained. Simplified protocols can be incorporated into an adapted approach that could be delivered by community health workers at home and that optimizes the use of ready-to-use foods. Further research should assess how simplified nutrition protocols can be part of the response to this need, optimizing existing resources to reach more children while maintaining a high level of clinical care for all sub-groups. Streamlined, cost-effective programs make a more persuasive case for future investment, and this in turn is more likely to result in public health impact at scale.

Supporting information

S1 Fig. Time to recovery for all children in per-protocol analysis.
(TIF)

S2 Fig. Time to recovery for all children in intention-to-treat analysis.
(TIF)

S3 Fig. Time to recovery for SAM children in per-protocol analysis.
(TIF)

S4 Fig. Time to recovery for SAM children in intention-to-treat analysis.
(TIF)

S5 Fig. Time to recovery for MAM children in per-protocol analysis.
(TIF)

S6 Fig. Time to recovery for MAM children in intention-to-treat analysis.
(TIF)

S1 Table. Standard ready-to-use therapeutic food dosage table.
(DOCX)

S2 Table. Comparison of combined and standard protocols.
(DOCX)

S3 Table. Admission characteristics of children by country.
(DOCX)

S4 Table. Coverage survey results by country, arm, and SAM/MAM status.
(DOCX)

S5 Table. Analyses of recovery and length of stay by sub-group.
(DOCX)

S1 Text. Procedures for taking anthropometric measurements.
(DOCX)

S2 Text. ComPAS study protocol.
(DOCX)

S3 Text. CONSORT checklist for cluster trials.
(DOCX)

S4 Text. CONSORT checklist for non-inferiority trials.
(DOCX)

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4.3 Paper IV: Results for Objective 3

Paper IV: **Bailey J,** Lelijveld N. Khara T, Dolan C, Stobaugh H, Sadler K, Lino Lako R, Briend A, Opondo C, Kerac M, Myatt M. Response to Malnutrition Treatment in Low Weight-for-Age Children: Secondary Analyses of Children 6–59 Months in the ComPAS Cluster Randomized Controlled Trial. Nutrients. 2021; 13, 1054. https://doi.org/10.3390/nu13041054**.**

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	173611	**Title**	Ms.
First Name(s)	Jeanette		
Surname/Family Name	Bailey		
Thesis Title	Simplified, combined protocol for acute malnutrition in children 6-59 months: the ComPAS randomized controlled trial		
Primary Supervisor	Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Nutrients: Bailey J, Lelijveld N. Khara T, Dolan C, Stobaugh H, Sadler K, Lino Lako R, Briend A, Opondo C, Kerac M, Myatt M. Response to Malnutrition Treatment in Low Weight-for-Age Children: Secondary Analyses of Children 6–59 Months in the ComPAS Cluster Randomized Controlled Trial. Nutrients. 2021; 13, 1054. https://doi.org/10.3390/nu13041054.		
When was the work published?	March 2021		
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This paper describes secondary analyses of the ComPAS RCT dataset to evaluate outcomes among children with severely low weight-for-age and/or severely low MUAC. The idea for this analysis came as a co-creation between myself and my co-authors from the Wasting Stunting Technical Interest Group (MM, TK, KS, CD, NL), with support from my ComPAS co-investigators (MK, CO, AB). I drafted the initial analysis plan and dummy tables and completed the final outcome analyses. My colleagues Dr. Mark Myatt and Dr. Lelijveld supported with preparation and cross-checking of the database, and Dr. Myatt conducted the growth curve analyses presented in Figure 2 and Supplementary Figure 1, and the Venn Diagram in Figure 3. I wrote the drafts, managed the revisions and prepared the paper for final publication in Nutrients.

SECTION E

Student Signature	Jeanette Bailey
Date	1 April 2021

Supervisor Signature	Dr Marko Kerac
Date	15th April 2021

nutrients

MDPI

Article

Response to Malnutrition Treatment in Low Weight-for-Age Children: Secondary Analyses of Children 6–59 Months in the ComPAS Cluster Randomized Controlled Trial

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Abstract: Weight-for-age z-score (WAZ) is not currently an admission criterion to therapeutic feeding programs, and children with low WAZ at high risk of mortality may not be admitted. We conducted a secondary analysis of RCT data to assess response to treatment according to WAZ and mid-upper arm circumference (MUAC) and type of feeding protocol given: a simplified, combined protocol for severe and moderate acute malnutrition (SAM and MAM) vs. standard care that treats SAM and MAM, separately. Children with a moderately low MUAC (11.5–12.5 cm) and a severely low WAZ (<−3) respond similarly to treatment in terms of both weight and MUAC gain on either 2092 kJ (500 kcal)/day of therapeutic or supplementary food. Children with a severely low MUAC (<11.5 cm), with/without a severely low WAZ (<−3), have similar recovery with the combined protocol or standard treatment, though WAZ gain may be slower in the combined protocol. A limitation is this analysis was not powered for these sub-groups specifically. Adding WAZ < −3 as an admission criterion for therapeutic feeding programs admitting children with MUAC and/or oedema may help programs target high-risk children who can benefit from treatment. Future work should evaluate the optimal treatment protocol for children with a MUAC < 11.5 and/or WAZ < −3.0.

Keywords: acute malnutrition; weight-for-age; mid-upper arm circumference; ready-to-use therapeutic food; community-based management of acute malnutrition; wasting; stunting; concurrent wasting and stunting

1. Introduction

Malnutrition is a major underlying cause of morbidity and mortality in children [1]. At any given time, stunting, defined by deficits in a child's height-for-age, affects at least 149 million children under five years of age, and wasting, defined by deficits in a child's weight-for-height and/or a low mid-upper arm circumference, affects about 49 million children [2]. The incidence of wasting in children may be far higher than these prevalence

estimates suggest [3,4]. Malnutrition contributes to approximately half of all deaths in children less than 5 years of age [1], and deaths associated with wasting may also be significantly underestimated [5]. The coronavirus pandemic is likely to further increase wasting and associated mortality [6].

Current policy and practice organize programs that focus on stunting and wasting separately [7–10]. Stunting is typically addressed through development programs that primarily focus on its prevention, whereas wasting is often addressed through humanitarian programs that primarily focus on its treatment in order to prevent near-term mortality. Multisectoral social and development programs aim to prevent stunting through agriculture; micronutrient supplementation; infant and young child feeding; and water, sanitation, and hygiene (WASH) approaches, among others [11]. The management of wasting may include therapeutic and supplementary feeding and treatment of underlying illnesses. Despite evidence of the common causal pathways for wasting and stunting [12,13] and the epidemiological overlap [14], programs rarely integrate objectives to address both forms of undernutrition simultaneously. Current funding mechanisms and organizational structures facilitate this division, with grants usually directed to programs addressing either stunting or wasting but seldom both [7]. In practice, this means programs addressing both wasting and stunting may not be available at the same place and time. Similar silos exist within wasting treatment, as severe and moderate acute malnutrition (SAM and MAM) are treated in separate programs [7,15].

Children with concurrent wasting and stunting are among the most vulnerable of all malnourished children, with a higher mortality risk than either wasting or stunting alone, and about a 12 times greater risk of mortality in the absence of treatment than those with normal anthropometry [16,17]. In low-income countries, 4.7% of children are affected simultaneously by wasting and stunting [18]. Acknowledging the coexistence of wasting and stunting and the interactive effect on mortality risk, recent research has explored existing data to understand more about this particularly vulnerable group. Existing measures used at the community level were evaluated for their ability to identify concurrently wasted and stunted children. Weight-for-age (z-scores from the international reference median, WAZ) was found to have high (i.e., >90%) sensitivity and specificity for identifying children who are concurrently wasted and stunted across multiple settings [17]. In an analysis of cohort data from Senegal, different anthropometric criteria were examined for their ability to predict mortality. A combination of a severely low mid-upper arm circumference (MUAC < 11.5 cm) and a severely low WAZ (i.e., WAZ < −2.8) detected all near-term (i.e., occurring within 6 months of measurement) deaths associated with either a weight-for-height z-score (WHZ) < −3 and/or concurrent wasting and stunting (WHZ < −2 and height-for-age z-score (HAZ) < −2) [19,20]. MUAC is already well evidenced to identify those at high risk for mortality and is easy to use [21–24]. Used together, these measures may be both practical and effective as MUAC and WAZ are already used at the community level for screening and for growth monitoring and promotion.

Current therapeutic feeding programs use MUAC < 11.5 cm, WHZ < −3 and/or presence of oedema as independent admission criteria [25,26]. Some children who are severely wasted and concurrently stunted are included by these criteria, but moderately wasted children who are concurrently stunted may not be captured for therapeutic feeding by these admission criteria despite their having a similar near-term mortality risk to severely wasted children [16,17]. Adding WAZ to the admission criterion for therapeutic feeding could improve the ability of these programs to identify and treat malnourished children most at risk of dying [19]. The intensity of treatment required by this additional group of children and the impact of their inclusion on therapeutic program caseloads and workload has yet to be evaluated in a prospective trial. There is already growing interest to simplify protocols for wasting treatment to reduce the silos between SAM and MAM treatment and optimize the use of resources to identify and treat the most vulnerable children [27–36]. Combining SAM and MAM treatment into a single protocol provides a holistic continuum of care that may enable treatment before children become severely malnourished. This pa-

per therefore draws on data from a randomized controlled trial that tested the effectiveness of a simplified, combined protocol for treatment of medically uncomplicated severe and moderate acute malnutrition in children aged between 6 and 59 months [27,35].

The aim of this analysis was to contribute evidence on the value of adding WAZ to therapeutic feeding program admission criteria. Our objectives were to (1) assess outcomes and response to treatment in children admitted with a MUAC < 11.5 cm as two separate groups—those with a WAZ <−3 and those with a WAZ ≥ −3—both of which would be included in current therapeutic feeding programs, as well as children with a moderately low MUAC (i.e., MUAC between 11.5 cm and 12.5 cm) and a WAZ < −3, who would be eligible for admission into supplementary feeding programs in many settings; (2) explore outcomes and response to treatment by dosage protocol: a simplified, MUAC-based dosage in a combined treatment program compared to the weight-based dosage offered in standard care.

2. Materials and Methods

This paper reports on a secondary analysis of the intention-to-treat dataset from the Combined Protocol for Acute Malnutrition Study (ComPAS). ComPAS was a cluster-randomized controlled trial conducted in Kenya and South Sudan from May 2017–August 2018 to evaluate whether a simplified, combined protocol was non-inferior to standard care for treatment of medically uncomplicated SAM and MAM in children 6–59 months. The trial found non-inferior recovery (76.3% in the combined protocol arm and 73.5% in the standard protocol arm, risk difference of 0.03, 95% CI −0.05 to 0.10, p = 0.52), with less ready-to-use food required for a child with severe malnutrition to reach full recovery in the combined protocol (122 versus 193 sachets) and improved cost-effectiveness (US$123 less per child recovered; US$918 in the combined protocol versus US$1041 in the standard protocol) [35]. The methods [27,37], scientific rationale [34] and results [35] from the ComPAS trial have been published previously.

This study was a secondary analysis of data from a trial conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the ethics committees of the London School of Hygiene and Tropical Medicine (reference 11826), the Kenya Medical Research Institute (reference non-KEMRI 551), and the Ministry of Health in South Sudan (approved 21 November 2016). The analyses conducted for this paper comply with these ethical approvals. Written informed consent was obtained from the caretakers of all patients or by a witness who could attest to the caretaker's verbal consent.

In standard treatment, SAM and MAM are treated in separate programs with separate food products [7,15]. SAM is treated with ready-to-use-therapeutic food (RUTF) based on weight, and MAM can be treated with one sachet of ready-to-use supplementary food (RUSF) per day (Table 1). In the ComPAS intervention arm, a simplified, combined protocol admitted children with both SAM and MAM for treatment in a unified program, with eligible children receiving RUTF according to their MUAC and/or oedema status (Table 1, Supplementary Table S1). A simple MUAC-based RUTF dosage protocol was used because of evidence showing that MUAC identifies children at high-risk of mortality and is easier to use than weight-for-height measures [21–24], and that changes in MUAC track changes in weight [34,38,39]. The simplified protocol provides a reduced dosage of RUTF for children with a MUAC < 11.5 cm who have an admission weight of ≥ 5 kg, as these children would have received 2.5 sachets/day under the standard protocol (Supplementary Table S2).

Table 1. Energy and food product given by treatment group.

Group	Combined Protocol	Standard Protocol
Group 1: MUAC < 11.5 cm and WAZ ≥ −3.0	4184 kJ (1000 kcal)/day RUTF	836.8 kJ (200 kcal)/kg/day RUTF
Group 2: MUAC 11.5 to <12.5 and WAZ < −3.0	2092 kJ (500 kcal)/day RUTF	2092 kJ (500 kcal)/day RUSF
Group 3: MUAC < 11.5 cm and WAZ < −3.0	4184 kJ (1000 kcal)/day RUTF	836.8 kJ (200 kcal)/kg/day RUTF
Group 4: MUAC 11.5 to <12.5 and WAZ ≥ −3.0	2092 kJ (500 kcal)/day RUTF	2092 kJ (500 kcal)/day RUSF

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score; RUTF, ready-to-use-therapeutic food; RUSF, ready-to-use supplementary food.

Clusters in the ComPAS trial were 24 health facilities stratified by country and randomized to deliver either the combined protocol or the standard protocol [27]. The dataset included children aged between 6 and 59 months at admission diagnosed with moderate or severe wasting and without medical complications in three urban sub-counties of Nairobi, Kenya (Embakasi North, Embakasi East and Embakasi West) and Aweil East, a rural, agro-pastoralist region of Northern Bahr El Ghazal state in South Sudan. Children presenting to any of the 24 health clinics participating in the study were eligible to enroll. Active case finding was also conducted to refer children with malnutrition. Participants in Kenya were invited to attend an appointment four-months post-discharge as part of a follow-up study.

An anonymized dataset using only key variables from the ComPAS trial was used for this analysis [40]. The variables included case ID, age, sex, date of visit, anthropometric measurements (MUAC, weight, height, WAZ, HAZ) and oedema at each visit, outcome (recovered, died, defaulted, transferred or early discharge), site code, and intervention code (standard or combined protocol). Morbidity, hospitalization, fat mass, and fat-free mass variables were used from the follow-up study dataset. The following categorizations and anthropometric cut-offs were used:

- Group 1: MUAC < 11.5 cm and WAZ ≥ −3;
- Group 2: MUAC between 11.5 cm and <12.5 cm and WAZ < −3;
- Group 3: MUAC < 11.5 cm and WAZ < −3;
- Group 4: MUAC between 11.5 cm and <12.5 cm and WAZ ≥ −3.0.

Groups 1–3 were the groups of interest in this analysis, and group 4 is presented for comparison. Groups 1 and 3 are currently included in therapeutic feeding programs for treatment of SAM because MUAC < 11.5 cm is a standard admission criterion. Groups 2 and 4 are eligible for supplementary feeding for treatment of MAM where provided under existing guidelines because MUAC is between 11.5 and <12.5 cm [25,26]. Groups 1 and 3 received RUTF at a fixed dose of 4184 kJ (1000 kcal) RUTF/day in the combined protocol and RUTF at a standard dose 836.8 kJ (200 kcal)/kg/day in the standard protocol. Groups 2 and 4 received 2092 kJ (500 kcal) RUTF per day in the combined protocol and 2092 kJ (500 kcal) RUSF per day in the standard protocol (Table 1) [27]. RUTF and RUSF are similar in their compositions, but there are some key differences, including the proportion of total protein derived from dairy. RUTF typically has 50% of protein derived from dairy, and RUSF may have 33% of protein derived from dairy [25].

For each patient group, we assessed outcomes following treatment, duration of stay, and velocity of weight and MUAC change from admission until discharge. Outcomes included recovery (MUAC of ≥12.5 cm and no oedema for two consecutive visits), defaulting (failure to attend for three consecutive visits), death (including deaths that occurred after defaulting), transfers to other facilities, transfers to inpatient care, non-response (i.e., still under treatment but without recovery at or before the 17th week of treatment, and defined as “non-recovered” in this analysis) and early discharges (i.e., discharges made in error by facility staff before meeting recovery criteria for two consecutive visits, or being discharged

as non-responders before the 17th week time limit). These issues are described in detail in the main trial paper [35]. We use the term "non-recovered" instead of "non-response" in this paper because there are some children who gained weight or MUAC and thus did "respond" to treatment but ultimately do not reach the recovery criteria. All outcome categories in the analysis were mutually exclusive.

In Kenya only, caregivers of all study participants were asked to return for a follow-up visit at four months following discharge. The outcomes assessed at this visit were anthropometry (weight, height, MUAC, and oedema), recent history of illness, and body composition using bioelectrical impedance analysis (BIA) [41]. For the body composition analysis, raw impedance data were converted to fat and fat-free mass (FFM) values (kg) using a calibration equation derived from healthy children aged 3 to 18 months in The Gambia [42].

Because the data came from a cluster-randomized controlled trial, outcome analyses were adjusted for clustering of observations within health facilities using a cluster-robust estimator of variance. We used binomial regression for binary outcomes and linear regression for continuous outcomes. Adjusted analyses accounted for country, age, and sex. Analyses were conducted using Stata IC v.13.1 (StataCorp LLC: College Station, TX, USA). Stata's zscore06 module was used to calculate weight-for-age z-scores and flags, using WHO 2006 Growth Standards [43]. Children with biologically implausible WAZ values as determined by WHO flagging criteria (WAZ > 5 or < -6) at admission were excluded [44,45], and children with oedema on admission were not included in this analysis because their weight-for-age on admission would be unduly high due to the oedema.

To develop individual growth curves, MUAC and weight-for-age were plotted at each visit and examined. One set of growth curves looks only at children who achieved recovery within 17 weeks, to allow for a closer examination of how these children recovered. cmAM programs typically report average weight and MUAC gains among recovered children only; therefore, this first set of growth curves is meant to align with cmAM reporting standards [46]. Another set of growth curves inclusive of all children was generated to assess overall trends in the study dataset. The overall pattern of growth was visualized using aggregate growth curves. Median MUAC or WAZ at admission and at each subsequent visit up to and including discharge were estimated using a non-parametric percentile bootstrap procedure with 10,000 bootstrap replicates. These estimates were plotted, and a summary growth curve fitted using a LOWESS smoother [47] that weighted the weekly median estimates by the square root of the sample size at each week in each group. Summary growth curves were made for groups 1–3 for both the combined and standard protocol programs.

3. Results

Of the 4078 children included in the ComPAS trial dataset [35], 58 were excluded. Of these, 47 did not have an admission WAZ calculated due to the presence of oedema (which would have biased weight and WAZ upwards), and 11 were excluded because they had implausible WAZ values [44,45]. A total of 4020 children were available for the outcome analyses. The growth curve analyses presented in Figure 1 included the 647 children in groups 1–3 who recovered within 17 weeks. Of these 4020 children, 1962 were in Kenya, and 780 (39.8%) returned for a four-month follow-up visit, of whom 225 were in groups 1–3 (Supplementary Table S3).

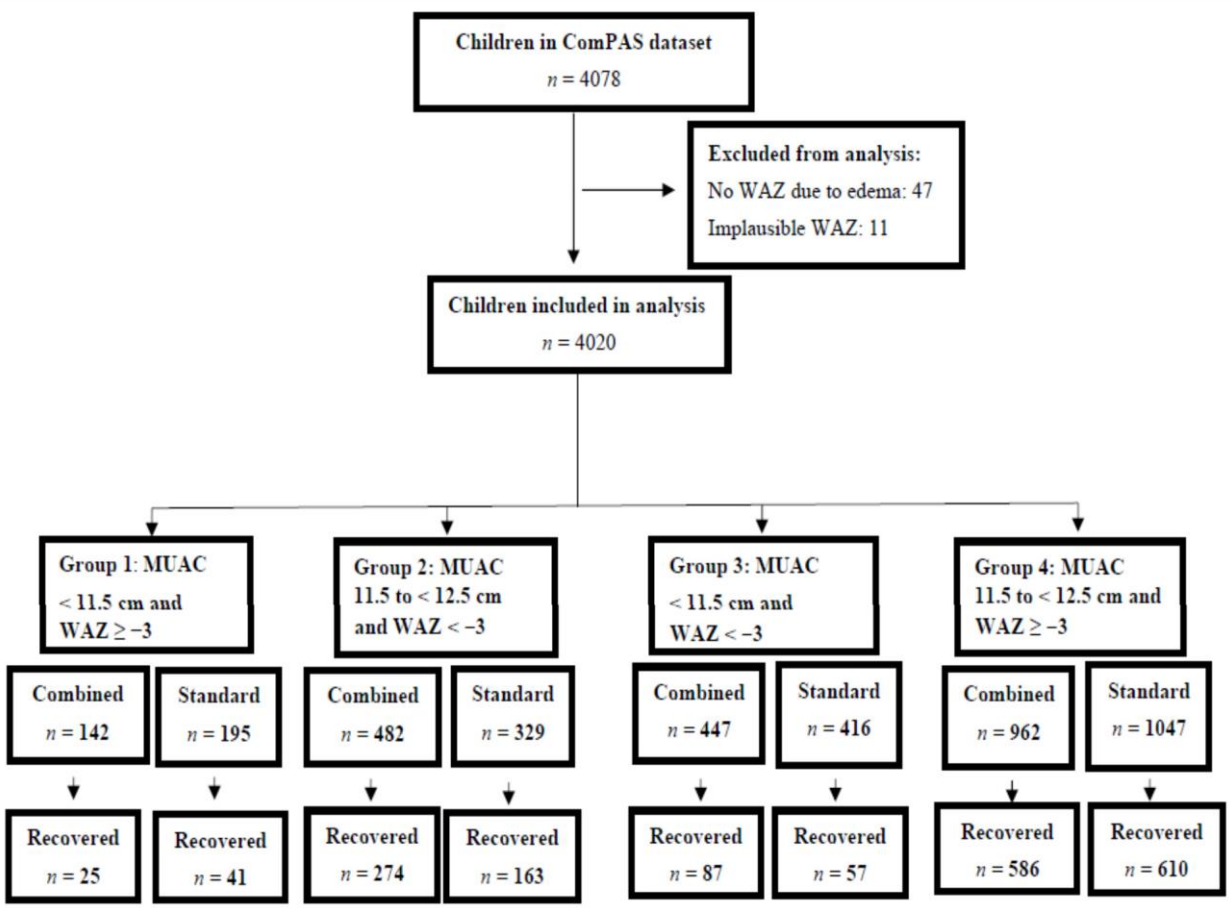

Figure 1. Analysis flow chart. MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score.

Half of the children in this analysis were either severely underweight (WAZ < −3) and/or severely wasted (MUAC < 11.5 cm) at admission. Of the 4020 children, 1674 (41.6%) had a WAZ < −3. Of the 1200 children with MUAC < 11.5 cm, 71.9% had a WAZ < −3. Among those with a WAZ < −3, 863, 51.6% had a MUAC < 11.5 cm, and 811 (48.4%) had a MUAC ≥ 11.5 cm. Of the 2820 children with MUAC ≥ 11.5 cm, 28.8% had a WAZ < −3. Twice as many children in South Sudan (66.9%) were either severely underweight and/or severely wasted than in Kenya (32.4%). A total of 21.5% of children were both severely underweight by weight-for-age and severely wasted by MUAC (Table 2).

Table 2. Numbers of children by category at admission.

Admission Groups	Total by Category	By Intervention Arm		By Country	
		Combined Protocol	Standard Protocol	Kenya	South Sudan
Group 1 MUAC < 11.5 cm and WAZ ≥ −3.0	337 (8.4%)	142 (7%)	195 (9.8%)	126 (6.4%)	211 (10.3%)
Group 2 MUAC 11.5 to <12.5 cm and WAZ < −3.0	811 (20.2%)	482 (23.7%)	329 (16.6%)	294 (15%)	517 (25.1%)
Group 3 MUAC < 11.5 cm and WAZ < −3.0	863 (21.5%)	447 (22%)	416 (20.9%)	215 (11%)	648 (31.5%)
Group 4 MUAC 11.5 to <12.5 cm and WAZ ≥ −3.0	2009 (50%)	962 (47.3%)	1047 (52.7%)	1327 (67.6%)	682 (33.1%)
Total	4020	2033	1987	1962	2058

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score.

Overall, 1150 (89.5%) of children with a WHZ < −2.0 and HAZ < −2.0 (i.e., concurrently wasted and stunted) also had a WAZ < −3.0. In Kenya, fewer children with a WHZ < −2.0 and HAZ < −2.0 also had a WAZ < −3.0 (80.9%). In South Sudan, more children with a WHZ < −2.0 and HAZ < −2.0 also had a WAZ < −3.0 (93.3%) (Table 3).

Table 3. Numbers of children at admission with a WHZ < −2.0 and HAZ < −2.0 identified by a WAZ < −3.0.

Country	Criterion	WAZ < −3.0	WAZ ≥ −3.0	Total
Kenya	WHZ < −2 and HAZ < −2	322 (80.9%)	76 (19.1%)	398
South Sudan	WHZ < −2 and HAZ < −2	828 (93.3%)	59 (6.7%)	887
Both	WHZ < −2 and HAZ < −2	1150 (89.5%)	135 (10.5%)	1285

WHZ, weight-for-height z-score; HAZ, height-for-age z-score; WAZ, weight-for-age z-score.

Group 1 were younger (median age 10 months) than the other groups and had the highest proportion of females. Group 2 were the oldest (median age 20 months), and Group 3 had a median age of 15 months (Table 4).

Table 4. Admission characteristics for the three patient groups of interest, by protocol type.

Characteristic	Group 1 MUAC < 11.5 cm and WAZ ≥ −3.0 (*n* = 337)		Group 2 MUAC 11.5 to <12.5 cm and WAZ < −3.0 (*n* = 811)		Group 3 MUAC < 11.5 cm and WAZ < −3.0 (*n* = 863)	
	Combined (m [§] = 12, *n* [†] = 142)	Standard (m = 12, *n* = 195)	Combined (m = 12, *n* = 482)	Standard (m = 12, *n* = 329)	Combined (m = 12, *n* = 447)	Standard (m = 12, *n* = 416)
Sex and Age						
Males, *n* (%)	31 (21.8%)	45 (23.1%)	258 (53.5%)	194 (59%)	221 (49.4%)	196 (47.1%)
Age at admission (months), median (IQR)	10 (8, 14)	10 (7, 14)	18 (12, 30)	21 (14, 30)	14 (9, 24)	15 (10, 24)
Age 6–24 months, *n* (%)	119 (83.8%)	168 (86.2%)	274 (56.8%)	173 (52.6%)	306 (68.5%)	287 (69.0%)
Anthropometry						
Weight (kg), mean (SD)	7.00 (1.54)	6.97 (1.62)	7.30 (1.42)	7.52 (1.39)	6.39 (1.34)	6.50 (1.31)
Height (cm) *, mean (SD)	72.6 (9.28)	72.0 (9.29)	74.0 (8.34)	74.9 (8.06)	70.8 (8.07)	71.5 (8.09)
MUAC (cm), mean (SD)	11.2 (0.23)	11.2 (0.29)	12.0 (0.27)	12.0 (0.26)	11.0 (0.44)	11.0 (0.49)
WAZ, mean (SD)	−2.4 (0.56)	−2.4 (0.52)	−3.6 (0.47)	−3.6 (0.52)	−4.1 (0.67)	−3.9 (0.66)
HAZ, mean (SD)	−0.91 (1.07)	−0.99 (1.16)	−3.05 (1.02)	−3.07 (1.03)	−3.13 (1.25)	−2.82 (1.17)
WHZ, mean (SD)	−2.61 (1.01)	−2.52 (0.73)	−2.72 (0.79)	−2.62 (0.81)	−3.23 (0.83)	−3.24 (0.86)

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score; HAZ, height-for-age z-score; WHZ, weight-for-height z-score.[§] m = number of clusters; [†] *n* = individual children eligible for treatment. * Length if child is <24 months.

In general, children with a MUAC < 11.5 cm (groups 1 and 3) had lower recovery and higher defaulting and non-response than children with a MUAC between 11.5 and <12.5 cm (groups 2 and 4) at admission. Within MUAC categories, severely underweight children had poorer outcomes than those without severe underweight. Of the three patient groups of interest, children in group 2 had the highest recovery (53.9%) and shortest length of stay (median 64 days), though recovery was lower and length of stay longer than for children in the comparator group 4 who had neither WAZ < − 3.0 nor MUAC < 11.5 cm (of whom 59.5% recovered with a median length of stay of 57 days). Recovery in group 1 was 19.6%, and this group had the longest median length of stay (94 days). Children in group 3 had the lowest recovery (16.7%), despite being 5 months older on average than group 1. Children in group 3 also had the highest proportion of defaulters (39.4%) and deaths (1.9%). Defaulting and non-recovery was high in all groups studied [35], though

group 2 had lower non-recovery (8.5%) and defaulting (21.7%) than groups 1 or 3. Among children with a MUAC between 11.5 cm and <12.5 cm, those with a WAZ <− 3.0 had lower recovery (Table 5)

Table 5. Outcomes of children, by admission category.

	MUAC < 11.5 cm				MUAC 11.5 to <12.5 cm			
Intention-to-Treat	**Group 1 MUAC < 11.5 cm and WAZ ≥ − 3.0 (*n* = 337)**		**Group 3 MUAC < 11.5 cm and WAZ < − 3.0 (*n* = 863)**		**Group 2 MUAC 11.5 to <12.5 cm and WAZ < − 3.0 (*n* = 811)**		**Group 4 MUAC 11.5 to <12.5 cm and WAZ ≥ − 3.0 (*n* = 2009)**	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Recovered *	66	19.6	144	16.7	437	53.9	1196	59.5
Died	3	0.9	16	1.9	7	0.9	18	0.9
Defaulted	131	38.9	340	39.4	176	21.7	480	23.9
Non-recovered †	102	30.3	225	26.1	69	8.5	176	8.8
Transfer-inpatient	9	2.7	29	3.4	10	1.2	8	0.4
Transfer-new facility	8	2.4	33	3.8	15	1.9	13	0.7
Early discharge	18	5.3	78	9.0	102	12.6	130	6.5
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Length of stay (days) ‡	94	73, 106	89.5	68, 101	64	43, 85	57	43, 76

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score.* Recovery is defined as MUAC ≥12.5 cm and no oedema for 2 consecutive visits. † Non-recovered is defined as not reaching recovery criteria after 17 weeks in treatment, even though some of these children achieved recovery after 17 weeks [35]. ‡ Length of stay among recovered children only, following global cmAM reporting standards [46].

In exploratory analyses of the sub-groups by type of protocol given, there was no evidence of a difference between the combined and the standard protocols for groups 1 or 2 for any of the outcomes (Supplementary Tables S4–S6). There was weak evidence of a difference by type of protocol given in group 3 in terms of recovery and defaulting. Recovery in group 3 was 19.5% in the combined protocol compared to 13.7% in the standard protocol (adjusted risk ratio = 1.36, 95% CI 0.90, 1.82, p = 0.07). Defaulting in group 3 was 33.6% in the combined protocol compared to 45.2% in the standard protocol (adjusted risk ratio = 0.74, 95% CI 0.57, 0.97, p = 0.03) (Supplementary Table S6). There was no evidence of a difference in mortality for children when treated with either the combined or standard protocol in any of the three groups (Supplementary Tables S4–S6).

Relapse to acute malnutrition at the four-month post-discharge follow-up visit in Kenya among children who were discharged as recovered in the three patient groups (n = 142) ranged from 8% to 25%. A high proportion of children who were admitted with MUAC < 11.5 cm and/or oedema reported an illness in the week before their post-discharge follow-up appointment (20–47%). Body composition (lean and fat mass) was similar for those treated with the combined and the standard protocol in each of the admission groups (Supplementary Table S3).

Growth curve analyses were conducted among recovered children in the three patient groups of main interest (Figure 2) and among all children (Supplementary Figure S1). The samples at each time point in the growth curves are small, and the 95% confidence bands between the combined and standard protocols mostly overlap, though there are some potential differences to highlight. Of children who recovered, WAZ gain appears slower and lower in Group 1 among children treated with the combined protocol (Figure 2a). There is no evidence of a difference in MUAC gain in this group. In Group 3, children in the combined protocol start out at a lower baseline for WAZ (Table 3), which may explain

some of the difference in Figure 2e. As with Group 1, there is no evidence of a difference in MUAC gain between the protocols in Group 3 (Figure 2f). In Group 2, the 95% confidence bands overlap for both WAZ and MUAC gain with no significant differences between the protocols.

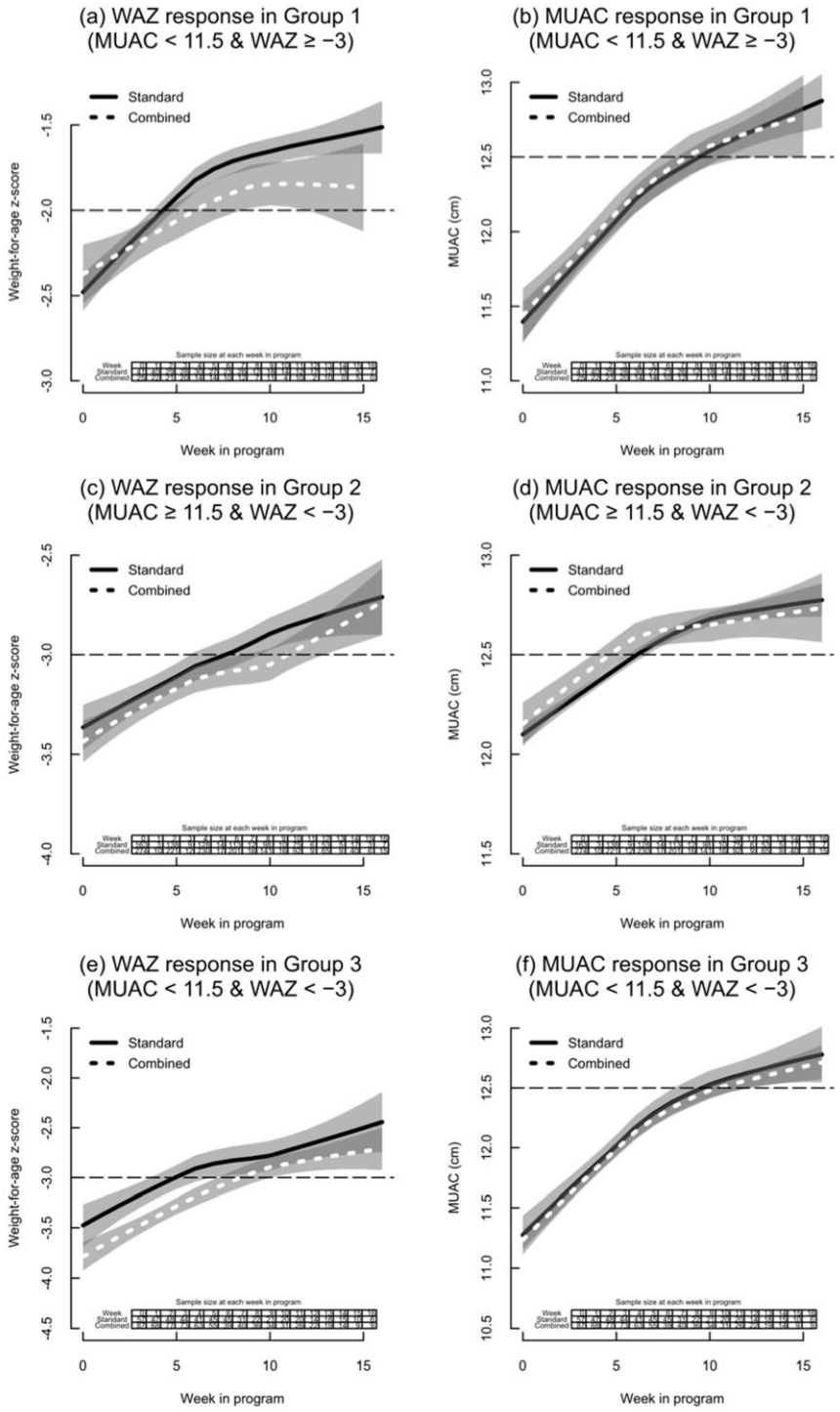

Figure 2. Panel of WAZ and MUAC response among recovered children by admission group. MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score. (**a**) WAZ plotted against week in program for Group 1; (**b**) MUAC plotted against week in program for Group 1; (**c**) WAZ plotted against week in program for Group 2; (**d**) MUAC plotted against week in program for Group 2; (**e**) WAZ plotted against week in program for Group 3; (**f**) MUAC plotted against week in program for Group 3. The shaded areas represent a 95% confidence band around each curve (i.e., the area between the upper and lower 95% confidence limits is shaded). Overlaps between confidence intervals are more darkly shaded.

Similar trends can be seen in the growth curves of all children, with lower WAZ gain in children treated with the combined protocol in Group 1 (Supplementary Figure S1a), though 95% confidence bands overlap at many time points, and there is no evidence of a difference in MUAC gain (Supplementary Figure S1b). In Group 2, the children in the combined protocol appear to start at a lower baseline and the overall shape, and trajectory of WAZ gain is similar to the standard protocol, with mostly overlapping 95% confidence bands (Supplementary Figure S1c). There is no evidence of a difference in MUAC gain between the protocols in Group 2 (Supplementary Figure S1d). In Group 3, children in the combined protocol start at a lower baseline WAZ (Table 3), and the curve remains lower at all time points (Supplementary Figure S1e). MUAC gain appears slower and lower among children in the combined protocol in Group 3 (Supplementary Figure S1f).

To assess how well a combination of WAZ < −3.0 and MUAC < 12.5 cm performs in capturing near-term deaths (i.e., within 6 months), we adapted an analysis of data presented in a previous paper [19] to assess a cut-off of WAZ <—3.0 instead of WAZ < −2.8 (Figure 3). A combination of MUAC and WAZ case definitions detect 39 (97.5%) of the 40 deaths associated with a WHZ < −3.0 and 62 (95.4%) of 65 deaths associated with concurrent wasting and stunting, as defined by WHZ < −2.0 and HAZ < −2.0 (WaSt).

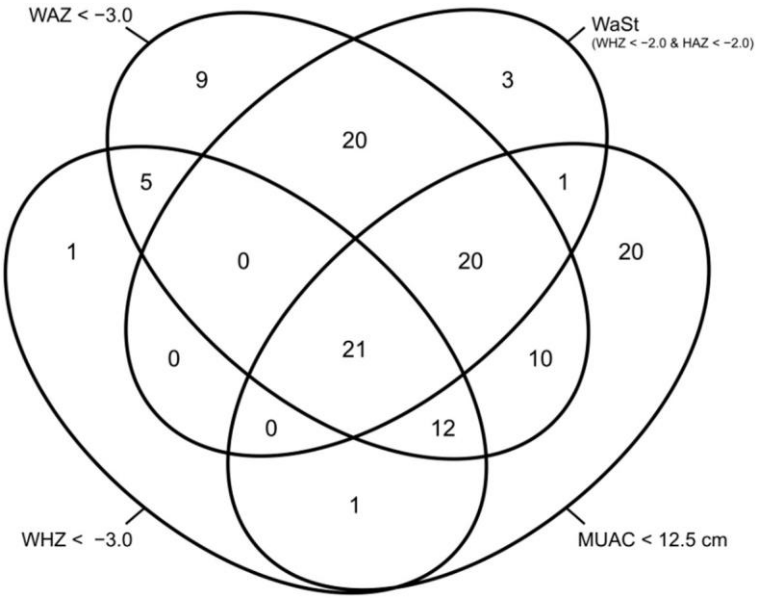

Figure 3. Venn diagram showing the number of deaths among treated children with different combinations of anthropometric deficits (adapted from Myatt et al., 2019 [19]). MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score; HAZ, height-for-age z-score; WaSt, both wasted and stunted.

4. Discussion

Children with a MUAC between 11.5 cm and <12.5 cm who would be admitted to therapeutic feeding programs if WAZ < −3.0 is added as an independent criterion had higher recovery and lower lengths of stay than either of the groups with a MUAC < 11.5 cm, despite receiving only a supplementary dose of RUTF or RUSF instead of a therapeutic dose based on weight. Recovery in this group remained lower than children with the same MUAC (between 11.5 to <12.5 cm) but a higher WAZ (i.e., WAZ ≥ −3.0), which may reflect the increased severity of their anthropometric deficits. Children who recovered in this group also achieved rapid growth under both the combined and standard protocols, suggesting we may expect good response to treatment with 2092 kJ (500 kcal)/day of either RUTF or RUSF. Children with severely low MUAC (<11.5 cm), with and without severe underweight (WAZ < −3.0), had low recovery by 17 weeks (Table 5). These children

also had the longest lengths of stay and the highest defaulting. Children with both a MUAC < 11.5 cm and a WAZ < -3.0 had the lowest recovery of any patient group, with the greatest number of deaths. There was no evidence of a difference in mortality for children when treated with either the combined or standard protocol in any of the three groups (Supplementary Tables S4–S6). This analysis indicates some potential differences in the way severely malnourished children respond to treatment between the combined and standard protocols, though these differences were mixed. There was weak evidence of higher recovery and lower defaulting among children with a MUAC < 11.5 cm and a WAZ < -3.0 treated with the combined protocol. Among children with a MUAC < 11.5 cm and a WAZ ≥-3.0, there was some indication that WAZ gain was slower and lower in the combined protocol, though MUAC gain was similar. These mixed results in children with the most severe deficits in MUAC and WAZ warrant further investigation to understand the growth patterns and optimal dosage protocol for these groups.

Limitations to this analysis included both statistical and operational constraints. Caution should be exercised when extrapolating these results as these are exploratory analyses of small sub-groups. This is a secondary analysis of data from a trial that was not powered for sub-group analyses but for combined multi-country estimates of overall recovery in each treatment arm. The majority of children in the ComPAS trial were aged 6–24 months, thus limiting generalizability to older children. The eligibility criteria for this trial were focused on MUAC and/or oedema; therefore, we cannot assess how WAZ would perform as an independent criterion if we had admitted all those with WAZ < -3 but normal MUAC and oedema status. Operationally, the ComPAS trial faced multiple challenges. Study operations were disrupted by a nurse's strike and repeated national elections in Kenya in 2017, and the rainy season interfered with the accessibility of some clinic sites in South Sudan [35]. These operational factors affected both study arms equally and contributed to frequent missed visits, longer lengths of stay, and higher numbers of children discharged as non-responders or defaulters. An outcome of "non-response" (defined as non-recovered in this analysis) was strictly applied to all children still in treatment after the cut-off of 17 weeks, though some of these children went on to recover after 17 weeks [35]. Low overall recovery was reported in the intention-to-treat analyses of the ComPAS trial due to high defaulting, though the main per-protocol analysis reported higher recovery than the intention-to-treat analysis (76.3% in the combined protocol and 73.5% in the standard arm) [35]. The high defaulting reduced the number of recovered children that could be analyzed in each of the three admissions groups in this analysis.

Strengths of this analysis included the multi-country nature of the trial, which contributes to the generalizability of results. Both rural and urban settings are included. Additionally, the data analyzed comes from a randomized controlled trial, with quality control measures in place to ensure high accuracy of data. The ComPAS trial provided a unique opportunity to evaluate WAZ response in different settings and in children with both SAM and MAM in the same dataset and to explore their outcomes by intensity of dosage and type of food product given [27].

This analysis contributes to a growing body of evidence on the utility of adding WAZ as an admission criterion for therapeutic feeding programs alongside MUAC and oedema [17,19,48]. As humanitarian and development actors and governments study the impacts of combined and simplified SAM and MAM programming [27–36], debate continues over which anthropometric indicators and cut-offs are likely to admit the highest-risk children that can be treated successfully with currently available therapeutic feeding products [21,49]. Given that a combination of low WAZ and/or low MUAC captures nearly all near-term mortality associated with anthropometric deficits including low WHZ and concurrent wasting and stunting, their combined use is an inclusive approach to therapeutic feeding admissions (Figure 3) [17,19]. In addition to being good predictors of near-term mortality, WAZ and MUAC are practical to use [19,22,23,50]. It is difficult to identify children with concurrent wasting and stunting and prioritize them for treatment because HAZ is not an admission criterion for therapeutic feeding. WAZ may be a more

feasible community-based alternative. Community-level programs can use WAZ to identify children with a severely low WHZ who are at high risk of mortality without needing to measure height [17,19]. WAZ and MUAC are already widely used in community programs (such as Expanded Program on Immunization (EPI), Integrated Management of Childhood Illnesses (IMCI), Growth Monitoring and Promotion (GMP), and community screening). WAZ integrates multiple anthropometric dimensions of malnutrition, thus bridging the current divide in programming between wasting and stunting. The use of WAZ and MUAC also aligns with recent recommendations for the identification of SAM in infants less than 6 months [51].

These potential benefits must be weighed against potential drawbacks, including the difficulties assessing age in feeding programs and the likely increase in caseload. Age may be challenging to assess objectively, as it may be based on reporting using seasonal or cultural event calendars. This may affect the ability to accurately assess WAZ for some children. Current treatment programs, particularly those including moderate wasting, may already capture many low weight-for-age cases (41.6% of children admitted in the ComPAS trial had a WAZ < −3.0) (Table 2). Based on the numbers in this analysis, if WAZ < −3.0 (with a MUAC < 12.5 cm) is added as a criterion to a cmAM program admitting children with a MUAC < 11.5 cm only, the caseload would increase by 1.68 times (in this program, from 1200 children with a MUAC < 11.5 cm to 2011 children with either a MUAC < 11.5 cm and/or a WAZ < − 3.0). This is similar to caseload change estimates made from simple simulations using population, prevalence survey, and program coverage data reported previously [19]. However, the exploratory analyses presented in this paper indicate this additional group of children appear to respond well to 1 sachet of either RUTF or RUSF a day and a clinic visit every other week instead of weekly, thus making this a potentially cost-effective approach. In emergencies or resource-constrained settings, either RUTF or RUSF could be selected based on availability. If this group of children identified by WAZ < −3 is added into a program using a simplified and combined protocol, additional cost savings may be seen. In this analysis, out of the 589 children with a MUAC < 11.5 cm (groups 1 and 3) treated with the combined protocol, 535 (90.8%) had an admission weight of ≥5 kg and thus received a reduced dosage of RUTF compared to standard care (Supplementary Table S2). Our prior research on this dosage protocol indicated it is sufficient to meet the theoretical energy needs of children 6–59 months recovering from uncomplicated acute malnutrition [34], and recovery was non-inferior to the standard protocol in an RCT [35]. The reduced dosage and other cost savings seen in a simplified protocol [30,35,36] may make it more feasible to treat additional children identified using WAZ and maintain the overall cost-effectiveness of the program.

Future work should evaluate how to treat children with the highest risk of mortality efficiently and effectively. This includes prospectively testing appropriate treatment regimens for the severely low MUAC and WAZ groups, assessing how adding WAZ to the admission criteria for therapeutic feeding affects caseload, resource use and workload, and evaluating outcomes of low weight-for-age and concurrently wasted and stunted children under treatment. Existing cmAM cohort data could be used for this purpose, as many SAM cases are likely to have a WAZ < −3.0 (Table 2). Future work could look at whether children who do not ultimately reach recovery criteria nonetheless improve their WAZ and MUAC. Different WAZ and MUAC cut-offs for admission and management can be tested according to context and in consideration of aggravating factors such as food insecurity and prevalence of disease. A WAZ < −3.0 identified different proportions of children with concurrent wasting and stunting in Kenya and South Sudan in this analysis (Table 3). Studies should build in adequate follow-up time post-treatment to assess longer-term growth trends and health outcomes of children with a low WAZ.

5. Conclusions

Preventing mortality and achieving optimal long-term health outcomes should be the goal of therapeutic feeding. This requires a more flexible view of what defines malnutrition

to avoid the silos created by SAM/MAM or wasted/stunted classifications. Adding WAZ as an admissions criterion may help programs target children at higher risk of adverse outcomes who may benefit from treatment. The optimal dosage protocol for the most severely malnourished (MUAC < 11.5 cm, with and without a WAZ <−3.0) should be evaluated further.

Supplementary Materials: The following are available online at https://www.mdpi.com/2072-6643/13/4/1054/s1. Table S1. Comparison of combined and standard protocols. Table S2. Standard ready-to-use therapeutic food dosage table (based on 200 kcal/kg/day using 92 g packets containing 500 kcal). Table S3. Relapse, body composition, and morbidity at four months post-discharge, by admission category and protocol type (Kenya sample only). Table S4. Outcomes of children in group 1, unadjusted and adjusted risk ratios. Table S5. Outcomes of children in group 2, unadjusted and adjusted risk ratios. Table S6. Outcomes of children in group 3, unadjusted and adjusted risk ratios. Figure S1. Panel of WAZ and MUAC response among all children by admission group.

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Institutional Review Board Statement: This study was a secondary analysis of data from a trial conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the ethics committees of the London School of Hygiene and Tropical Medicine (reference 11826), the Kenya Medical Research Institute (reference non-KEMRI 551), and the Ministry of Health in South Sudan (approved 21 November 2016). The analyses conducted for this paper comply with these ethical approvals.

Informed Consent Statement: Written informed consent was obtained from the caretakers of all patients or by a witness who could attest to the caretaker's verbal consent.

Data Availability Statement: Underlying data and code for this paper are available via https://datacompass.lshtm.ac.uk/1151/. The full dataset cannot be made open access due to the presence of participant identifiable content. A redacted version will be provided to interested parties, subject to the completion of a request form (available via the repository link above) and signing of a Data Transfer Agreement.

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Chapter 5: Discussion

5.1 Summary of research findings

The aim of this thesis was to generate evidence on a simplified, combined SAM and MAM approach to treat uncomplicated acute malnutrition in children 6-59 months, using a MUAC-based RUTF dosage protocol. Each stage of the research contributed different findings to our understanding of managing uncomplicated acute malnutrition in children 6-59 months. Below is a summary of key findings as they relate to the three objectives of this thesis.

> **Objective 1:** Assess MUAC and weight gain trends in children recovering from acute malnutrition and estimate energy requirements correlated with MUAC category, to inform the development of a simplified, MUAC-based dosage protocol for SAM and MAM.

In the first stage of the research, we found that children with a MUAC <12.5 cm need approximately 1,000 kcal/day to achieve optimal growth during treatment. The rate of MUAC and weight gain appear to slow when children reach a MUAC of approximately 11.5 cm, and thus we proposed a reduction in the dosage from 1,000 kcal/day (2 sachets) of RUTF to 500 kcal/day (1 sachet) of RUTF when children reached a MUAC of 11.5 cm and no oedema for two consecutive visits, in line with global guidance on the management of MAM.[23, 24] These findings were theoretical, and the next stage was to test this protocol in a field setting.

> **Objective 2:** Evaluate if the simplified, combined protocol is non-inferior to the standard protocol in terms of recovery and assess whether it improves cost-effectiveness.

In the second stage of the research, we found that a simplified, combined protocol is as effective as standard treatment and saves money. A MUAC-based dosage protocol providing 1,000 kcal/day (2 sachets) of RUTF for children with a MUAC <11.5 cm and/or oedema, and 500 kcal/day (1 sachet) of RUTF for children with a MUAC between 11.5 cm and <12.5 cm, is as good as the standard weight-based dosage protocol in terms of anthropometric recovery. Less RUTF is required to fully recover a child admitted with SAM (122 vs. 193 sachets). Stream-lined logistics and program management introduces additional cost savings, particularly in the South Sudan context, where the RUTF and RUSF supply chains were managed separately.

Objective 3: Explore the outcomes of subgroups of children with severely low weight-for-age and/or severely low MUAC, to contribute evidence on the optimal dosage required by children who may be at a high risk of near-term mortality.

In the final stage of the research, we found that children with a MUAC between 11.5 and <12.5 cm and a WAZ <-3.0 respond similarly to either 500 kcal of RUTF or 500 kcal of RUSF. This group with a WAZ <-3.0 but a MUAC ≥11.5 cm is currently excluded from therapeutic feeding programs, and evidence from this analysis indicates they benefit from a low intensity treatment. Children with a severely low MUAC <11.5 cm, with or without a WAZ <-3.0, have the poorest outcomes, with similar recovery, MUAC gain and mortality between the combined and standard protocol groups. Among children with a MUAC <11.5 cm and a WAZ ≥-3.0, there is some indication WAZ gain may be slower in the combined protocol. The optimal dosage protocol for children with a MUAC <11.5 cm, with or without a WAZ <-3.0, should be confirmed with further research.

5.2 Research in context

These findings are similar to related trials.[31, 32, 87] The simplified and combined management of SAM and MAM in a single protocol achieves similar numbers of recovered children and contributes to cost savings.[31, 32, 132] When used at a larger scale over a longer timeframe in an operational study, a combined SAM/MAM treatment protocol may reduce the SAM caseload, by preventing children with MAM from deteriorating into SAM.[32] Reduced dosages of RUTF provided to children with SAM results in similar recovery, average daily weight and MUAC gains,[31, 32, 86, 87, 132] though one trial indicated a negative impact on height gain.[87] The ComPAS follow-up study (Annex J) found no difference in relapse among children treated with the simplified, combined protocol compared to the standard protocol, or in body composition four months post-discharge, similar to findings from the Treat Food trial in Burkina Faso.[76]

5.3 Strengths

5.3.1 Technical strengths

The design of ComPAS with multiple stages allowed for an extensive development and theoretical testing phase prior to its practical application in a field RCT setting. In addition to two distinct

research stages, ComPAS comprised multiple sub-studies including the cost-effectiveness analysis, the follow-up study on body composition and relapse, and a policy landscaping analysis.[133]

Objective 1 was answered with a large database from five countries, allowing for greater confidence in the choice of RUTF rations as the MUAC-based dosage protocol was developed.

Objectives 2 and 3 were answered with data from the RCT, which is considered as a strong source of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[134]

The ComPAS RCT was designed to compare against the 'gold standard' of standard care for CMAM: integrated OTP and SFP services offered in the same physical location, with RUSF offered for MAM instead of fortified blended flours. In many situations, the reality of 'standard care' is that treatment for MAM is not available, or only fortified blended flours are available for MAM, or treatment for SAM and MAM are not offered in the same location. ComPAS was designed to compare against the ideal implementation of CMAM to assess the value added of simplifying and combining treatment, and not just providing MAM treatment. This may also be seen as a limitation to the trial, as the true effect of offering a combined SAM and MAM protocol may be underestimated when the reality in many situations is that there is no MAM treatment at all.

5.3.2 Contextual strengths

The study benefited from the inclusion of data from multiple countries across several settings. The first stage drew on data from five countries in multiple regions: Chad, South Sudan, Kenya, Yemen and Pakistan. The RCT was conducted in two countries with very different contexts: rural South Sudan and urban Kenya. The diversity of data increased the generalizability and applicability of the results across both rural and urban contexts.

5.3.3 Research into policy and practice

The ComPAS research benefited from a global coalition of research partners, an expert scientific committee and the engagement of key policy stakeholders, including UN agencies, institutional donors and Ministries of Health. The engagement of key stakeholders helped position the research

to directly inform future policy discussions. The global coalition of partners that supported ComPAS connected the study team to a diverse range of technical expertise and policy perspectives.

5.4 Limitations

Different limitations impacted each component of the ComPAS research.

5.4.1 Secondary analysis of routine program data

In the first stage, the analysis of rate of growth and energy requirements was based on retrospectively collected routine program data from three different agencies, across multiple countries and years. Children in the dataset were treated in different types of feeding programs, but we did not have information on the type or amount of food product offered to children with MAM. In South Sudan, only children with SAM were admitted, though these children were treated until they recovered from MAM (MUAC >12.5 cm). Therefore, for children with a MUAC between 11.5 to <12.5 cm, the type of treatment they received differed according to context. For example, a child in South Sudan admitted to a SAM-only treatment program would be treated with a weight-based dosage (175-200 kcal/kg/day) even after their MUAC qualified them as MAM (11.5 to <12.5 cm). A child with a similar MUAC admitted to a MAM treatment program in one of the other four countries may have been treated with a single sachet of RUSF/day, or with fortified blended flours. Data on specific subgroups were limited in the stage 1 database- particularly older, larger children with SAM (defined as ≥24 months and/or ≥8kg with a MUAC <11.5 cm and/or oedema), and therefore care should be taken in extrapolating results to these subgroups.

5.4.2 Randomized controlled trial in Kenya and South Sudan

The RCT took place in two countries, but neither country-specific sample size was powered to be large enough for an independent country subgroup analysis of results. This was due to funding restrictions. The original donor for the trial wanted to see results from different countries to increase generalizability, but there was not enough funding to increase the size of the trial. Multiple operational limitations including a national nurse's strike, national elections and a rainy season

affected the trial; these are described in detail in Paper III. These factors contributed to high defaulting across both arms of the trial, and likely also increased the average length of stay and decreased the average weekly weight and MUAC gains.

As with the secondary analysis of routine program data in first stage of research, the majority (approximately 75%) of children in the RCT were between 6-24 months. The results are therefore less generalizable to older children >24 months, as there were not enough of them to specifically explore or compare the outcomes for this group. The results are generalizable to CMAM programs overall as the age of participants was similar to many programs globally, but caution should be taken assuming the dosage tested will work across all age ranges equivalently.

Similarly, the RCT was conducted in two East African contexts, and more research is needed to assess the effectiveness of a reduced dosage protocol in other geographic contexts. Different dosage protocols, using different anthropometric cut-offs, may be appropriate in African vs. Asian or food insecure vs. food secure contexts.[88] Paper II of this thesis found that the amount of energy required for recovery of children with a MUAC <11.5 cm in the Asian countries may be lower than in the African countries included in the analysis, consistent with research indicating SAM may be different in children in Asian vs. African contexts.[135]

5.4.3 Cost-effectiveness analysis

The cost-effectiveness results were limited in scope, varying significantly by context and by severity of acute malnutrition. In South Sudan, with a higher proportion of SAM children, greater cost savings were seen due to the reduced dosage of RUTF provided to some children with SAM. In Kenya, these savings due to RUTF costs were not apparent due to a smaller proportion of SAM. Similarly, in Kenya a national logistics system, the Kenya Medical Supplies Agency (KEMSA) manages both the supply of RUTF and RUSF, reducing the potential of a single product to improve cost efficiencies. In South Sudan, where RUTF and RUSF are supplied through separate UN agencies (UNICEF for RUTF and WFP for RUSF), the effect of a combined protocol with a single food product improved cost savings. The cost results were limited by these country-specific differences because the overall intention-to-treat recovery rate was used to assess cost-effectiveness, but a country-specific estimate of recovery would have improved our understanding of cost-effectiveness in each context.

5.4.4 Secondary analysis of children with low weight-for-age

Limitations to the secondary analysis of children with low weight-for-age included the operational constraints for the trial described above, as well as the statistical constraints of analyzing a subgroup of children that the sample size was not powered to investigate. The eligibility for the ComPAS trial was based on MUAC and oedema, therefore we cannot evaluate the outcomes of children who may have had a WAZ <-3.0 but a MUAC >12.5 cm and no oedema. We are not able to contribute evidence on the use of WAZ <-3.0 as an independent criterion for admissions to therapeutic feeding programs, nor do we know how many children might have qualified under such a criterion as this data is not routinely collected.

5.5 Current context and policy implications

5.5.1 Inspiring new research

The ComPAS research and related studies[31, 87, 129] contributed to a shift in thinking about SAM and MAM treatment, helping to inform and inspire new and related research [20, 32-35, 136-140] and a community of practice on simplified approaches.[141] A Simplified Approaches Working Group, led by UN and NGO nutrition partners, was formed in 2019 to support the uptake of the simplified, combined protocol and related approaches globally. New studies have looked at optimizing the dosage of RUTF offered to children during SAM treatment,[32, 83, 87, 132] combining SAM and MAM treatment,[31, 32, 34, 132] and simplifying treatment overall.[31-34, 59, 132, 138, 142] Some elements of the protocol studied in ComPAS remain debated, particularly MUAC-only programming,[58] the appropriate dosage[83] and the extension of treatment to all children with MAM.[25] Overall, there is a drive towards better understanding which children need what kind of treatment and how to optimally identify and support them.[142-146]

5.5.2 Informing UN and institutional donor guidelines

As a result of ComPAS and related research, several UN agencies and institutional donors have released guidelines encouraging the use of simplified and combined programming, particularly in emergencies. In 2017, the Global Nutrition Cluster released an updated version of the MAM Decision

Tool for Emergencies, which included an adapted version of the ComPAS protocol for use in exceptional circumstances.[24] ECHO issued a technical issue paper on the simplified protocol in 2017 and OFDA incorporated guidance on simplifying and combining SAM and MAM treatment in their proposal guidelines in 2018.[147, 148] UNICEF released a statement outlining plans to shift treatment of wasting to use elements of the simplified, combined protocol, in combination with complementary interventions.[149] The COVID-19 pandemic accelerated the use of the simplified, combined protocol. UNICEF and the WHO released guidelines on the management of wasting in communities affected by COVID, recommending elements of the ComPAS protocol, such as MUAC-only programming, expanded admissions to all children with a MUAC <12.5 cm and/or oedema, and the use of a single RUTF product for both SAM and MAM.[150] UNICEF, the IRC and NGO partners published a complementary toolkit to support implementation of community health worker delivery of the simplified, combined protocol in the context of COVID-19.[151]

5.5.3 Piloting the simplified, combined protocol

UN agencies and institutional donors have also funded operational research of the ComPAS protocol. In 2018, UNICEF, WFP and ECHO organized operational research of the ComPAS protocol in West and Central Africa.[139] Pilots of the ComPAS protocol were initially implemented by the IRC in Mali and Chad in 2018 and 2019. These pilots were followed by more operational research run by UN agencies and NGO's in different countries and regions. According to the Simplified Approaches Working Group in February 2021, the ComPAS protocol was being tested or planned for use by seven different NGO's (IRC, AAH, MSF, Alliance for International Medical Action (ALIMA), Save the Children, GOAL, and Concern Worldwide) in more than 12 countries, including in Burkina Faso, Mali, Senegal, Afghanistan, South Sudan, Ethiopia, Chad, Somalia, Kenya, Niger, Mauritania and the Central African Republic.[139] The ComPAS protocol has been used in emergency responses in South Sudan, Nigeria, and Uganda among other countries.[152-154] UNICEF and WFP have committed to introducing simplified approaches in the Sahel and Horn of Africa regions, with a strong learning agenda to inform expansion to new regions.[155]

5.5.4 Reviewing the evidence in global consultations

The World Health Organization hosted a meeting to review the evidence on combined and simplified protocols in March 2019 and issued a statement.[143] The Field Exchange, a technical publication on nutrition and food security in emergencies, produced a special issue in 2019 focusing on the continuum of care, which highlighted research on simplified and combined protocols and approaches to improve SAM and MAM treatment along a continuum.[146, 156] In 2020, the UN released the Global Action Plan on Child Wasting with an extensive research agenda that included a call for more research on specific elements of simplified and combined protocols, including the optimal dosage and simplifications aimed at improving the cost-effectiveness and coverage of programming.[140] UNICEF published a rapid review of the evidence on simplified approaches in 2020, finding that the protocol used in ComPAS was the most widely used dosage adaptation, likely due to its simplified calculation of dosage based only on MUAC.[139] As part of the Global Action Plan on Wasting, the WHO committed to reviewing the evidence and revising the guidelines for treatment and prevention of wasting by the end of 2021.[140] The WHO commissioned scoping reviews and ComPAS and related studies were presented in a WHO Guideline Development Group meeting in December 2020.

5.5.5 Advocating for policy change

As researchers and programmers began to test simplified and/or combined CMAM programs that treated SAM and MAM in a single program, complementary advocacy efforts emerged to promote a more enabling global and national policy environment. Research addressing the continuum of care contributed to a wave of advocacy, driven by non-governmental organizations seeking a more efficient and effective UN system for managing acute malnutrition.[143, 157-160] A system that divides UN agency responsibility along SAM/MAM lines is no longer fit for purpose as the evidence for simplified, combined protocols increases in different contexts.[139, 161] Responding to the evidence and advocacy for improved coordination between the UN agencies on SAM and MAM, UNICEF and WFP committed in November 2020 to a new partnership agreement for the streamlined delivery of wasting treatment with a single agency lead.[162] Under the new system, UNICEF will take the lead on the management of wasting (both SAM and MAM) and WFP will provide support by providing food aid assistance and supply chain management in fragile contexts. This represents a paradigm shift in

how the UN manages wasting, promoting an integrated vision for the management of SAM and MAM.

5.5.6 National uptake

Despite the growing evidence and the momentum at a global level, national policies remain largely unchanged. In many emergencies, separate SAM and MAM programming remains the only option to remain in line with national protocol. Simplified, combined approaches are still primarily used at a small-scale in the context of operational research settings or short-term emergency responses.[24, 152-154] A review of national perspectives and policy on the combined protocol in 2018 indicated that though national government stakeholders generally agreed on the logic of offering SAM and MAM treatment in the same location and that using a single food product made logistical sense, there were concerns about using MUAC and oedema as the sole anthropometric admissions criteria and concerns about maintaining the supply chain for RUTF. Interest in a simplified and combined SAM/MAM protocol is increasing from Ministries of Health and nutrition partners in countries with a high burden of acute malnutrition, and national policy makers have sought more evidence and formal guidance from the WHO.[133, 163]

5.5.7 A shifting paradigm

Overall, the paradigm is shifting towards a greater acceptance of simplifying treatment and combining SAM and MAM programming, as evidenced by new research,[139] operational programming, UN and donor guidance,[24, 149, 150] and UN commitments.[140, 162] The national policy environment is shifting more slowly, and formal guidance from the WHO remains pending.[133] The United Nations agencies involved in nutrition are evaluating the evidence on simplified approaches[139, 143] and undergoing administrative re-alignments that may accommodate the simplified, combined protocol and other innovations in the sector through the Global Action Plan,[140, 162] though it remains to be seen whether this will translate into improved coverage of treatment for acutely malnourished children.

5.6 Further research

The optimal protocol will achieve a balance between simplifying CMAM to improve cost-effectiveness and coverage, while ensuring programs meet the needs of the most vulnerable children and adapting to the context.

5.6.1 Ensuring the protocol works for high-risk children

Children at an increased risk of mortality and long-term adverse outcomes should be the priority for treatment, and future research should focus on how best to identify and treat them. Malnutrition treatment programs should aim to prevent child mortality, and not just treat 'thinness.'[144] Malnourished children at the highest risk of mortality may include the youngest children (<24 months), those with concurrent wasting and stunting, multiple severe anthropometric deficits, severely low weight-for-age, and underlying medical conditions.[27-29, 45, 48, 59, 144] Future studies of the simplified, combined protocol should be powered to evaluate specific subgroups- particularly children at high risk of adverse outcomes and older, larger children with SAM- to ensure the dosage provided in a simplified protocol is sufficient for optimal growth and supports longer-term health and development outcomes.

There is also the question of how the dosage provided in ComPAS impacts indicators related to stunting, such as WAZ and HAZ. Though this research did not find any evidence of a difference between the simplified, combined protocol and standard treatment in terms of wasting response, the potentially slower WAZ gain found in Paper IV raises the possibility that other factors, such as stunting or age, may influence treatment response.

5.6.2 Adapting to the context

Contextual issues should also drive the identification and targeting of high-risk children, as children living in communities affected by chronic food insecurity, conflict, climate change and disease outbreaks are more vulnerable to malnutrition.[164] Identifying children who are physiologically vulnerable, as well as targeting children who live in geographically vulnerable contexts, may help programs direct resources where they are needed the most.

Future work will need to test adaptations of the protocol to fit the local context and circumstances. Operational research programs may adjust the protocol to add flexibility according to the context, using different ready-to-use food products, such as new formulations of RUTF of RUSF[76, 136] and/or integrating different cut-offs for admissions criteria.[57]

Though RUTF was used for the ComPAS research, future work could look at the operational and economic implications of using RUTF, RUSF or both in a simplified, combined approach. In early 2017, when the ComPAS trial was set to start, near-famine conditions were declared in four countries, including in South Sudan. The ComPAS research teams in both Kenya and South Sudan were unable to procure a sufficient supply of RUSF for several months due to a global supply shortage in RUSF. Unpredictable contextual and supply chain issues necessitate flexibility in humanitarian situations, and evidence on the optimal product(s) to use as part of this approach will help inform decision-making.

5.6.3 Adjusting the admissions criteria

Weight-for-age may be added as an independent criterion to improve detection of the highest-risk children.[28, 29] MUAC cut-offs may be adjusted to capture more or fewer children depending on the resources available.[152] Weight for-height may also be integrated in a simplified protocol, following the same dosage rules for severe (WHZ <-3.0) and moderate (WHZ <-2) malnutrition as the ComPAS protocol.[24]

5.6.4 Moving towards long-term and large-scale operational research

A next step is to pilot the ComPAS protocol at a large-enough scale and over a long-enough time to see how it works operationally in different contexts, among different subgroups of children, and assess its ability to reduce SAM over time, increase coverage and improve cost-effectiveness.

5.7 Conclusion

A simplified, combined SAM and MAM approach, using a MUAC-based RUTF dosage protocol, shows promise to maintain a high quality of treatment, save money, and thus potentially reach more children for similar resources. However, a simplified and combined protocol is just one solution among many to improve the coverage of treatment globally. The greatest impact will likely be seen when used in combination with complementary interventions, like the delivery of treatment through community health workers,[165-167] the training of caregivers to screen and refer their own children using MUAC and other tools,[72, 73, 168] and linkages to approaches that prevent malnutrition. A treatment approach that integrates caregiver screening and a treatment delivery model that utilizes community health workers at the village level may empower families and communities to identify and address malnutrition in children before it becomes severe. These approaches enable care to be delivered outside of health facilities, reducing the opportunity cost of seeking treatment for families that live far from medical care. A simplified, cost-effective, and community-empowered approach to treatment is crucial in an era when a global pandemic threatens the health and economies of vulnerable communities worldwide.[7] There are many challenges to scaling up a more community-centered approach to treatment, including ensuring a consistent and localized supply chain of ready-to-use foods, but these challenges can be surmounted with strategic partnerships that make use of strengths from the humanitarian, public and private sectors.

Ultimately, by making treatment simpler and more cost-effective to deliver, health systems may be better able to provide treatment at scale. If we can reach more children with MAM before they deteriorate into SAM, we can get further upstream of the problem- saving more money as a less intensive, less medicalized approach works well for children when they are less severely malnourished. With each step further upstream, we free up more resources to address malnutrition before it begins- investing more in prevention and working more on the underlying and systemic causes that cause malnutrition to begin with. Treatment is just the tip of the iceberg but remains crucial to unlocking the extraordinary potential of millions of lives saved- children who may one day become the most effective drivers of change to prevent childhood malnutrition in the future.

Annexes

A: Narrative review search strategy

Table A-1: Search terms

A. Integrated Treatment of Acute Malnutrition A1 + A2		**And /or**	**B. MUAC-only treatment of acute malnutrition B1+B2**		**And /or**	**C. RUF/Treatment for MAM C1+C2**		**Or**	**D. Energy needs during recovery from AM in children <5 D1+D2**	
A1	A2		B1	B2		C1	C2		D1	D2
"Integrat*Treat*" "Integrat*Manage*" "Combine*Treat*" "Combine*Manage*"	"Acute Malnutrition" "SAM and MAM" "severe and moderate acute malnutrition" "severe acute malnutrition and moderate acute malnutrition"		"Mid-upper arm circumference" "mid upper arm circumference" MUAC "MUAC-only" "MUAC only"	"Acute Malnutrition" "SAM and MAM" "severe and moderate acute malnutrition" "severe acute malnutrition and moderate acute malnutrition" "severe acute malnutrition" "moderate acute malnutrition" SAM MAM		"Ready-to-use food" "ready to use food" "Plumpy nut" "Ready-to-use supplementary food" "Ready-to-use therapeutic food" "Lipid nutrient supplement" "lipid-based nutrient supplement" LNS RUTF	"Moderate acute malnutrition" MAM		"energ*" "energy* needs" "energ* requirements" "calori*" "calori* needs" "calori* requirements"	"Acute Malnutrition" "SAM and MAM" "severe and moderate acute malnutrition" "severe acute malnutrition and moderate acute malnutrition" "severe acute malnutrition" "moderate acute malnutrition" SAM MAM

B: Ethical approvals

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Observational / Interventions Research Ethics Committee

Ms Jeanette Bailey
LSHTM

13 December 2016

Dear Jeanette,

Study Title: Combined Protocol for Acute Malnutrition Study (ComPAS) Stage 1: Secondary Data Analysis

LSHTM Ethics Ref: 11820

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	Rachel Chase_CV_Sept 2015	30/09/2015	final
Investigator CV	CV_Dr Marko Kerac_2016_07	03/07/2016	1
Protocol / Proposal	Statistical Analysis Plan_Stage 1_LEO	26/07/2016	3
Protocol / Proposal	OFDA Research Proposal Revised_July 30	26/07/2016	final
Investigator CV	Jeanette Bailey- CV	27/07/2016	final
Investigator CV	Mark Manary_CV	27/07/2016	final
Investigator CV	Andre Briend_CV	27/07/2016	final
Investigator CV	Charles Opondo_CV	30/07/2016	final
Local Approval	MSF France Data Sharing Agreement	14/09/2016	1
Local Approval	ACF-USA Sub-grant Agreement	14/09/2016	1
Local Approval	Attachment 2 Scope of Work	14/09/2016	1
Covering Letter	Cover letter_Response to LEO Stage 1_15 Sep_Signed	15/09/2016	2
Covering Letter	Cover letter_Response to LEO Stage 1_6 Dec	06/12/2016	1
Local Approval	MSF Data Sharing Policy	06/12/2016	1
Local Approval	MSF Research Ethics Framework	06/12/2016	1
Local Approval	MSF Ethics Review Board exemption letter for ComPAS	06/12/2016	1
Local Approval	MSF Ethics Review Board Standard Operating Procedures	06/12/2016	1
Local Approval	MSF France Written Permission to use Dataset	06/12/2016	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
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Observational / Interventions Research Ethics Committee

Ms Jeanette Bailey,
LSHTM

28 November 2016

Dear Jeanette,

Study Title: Combined Protocol for Acute Malnutrition Study (ComPAS) Stage 2: Cluster Randomized Controlled Trial

LSHTM Ethics Ref: 11826

Thank you for responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	ComPAS data collection matrix_1 June 2016_v2	01/06/2016	2
Protocol / Proposal	ComPAS_Analysis Plan Stage 2_v4_20 July	20/07/2016	4
Investigator CV	Jeanette Bailey- CV	27/07/2016	final
Investigator CV	Andre Briend_CV	27/07/2016	final
Investigator CV	Mark Manary_CV	27/07/2016	final
Investigator CV	Pamela Onyoo_CV	28/07/2016	1
Investigator CV	Bethany Marron_CV	28/07/2016	1
Investigator CV	CV_Dr Marko Kerac_2016_07	03/08/2016	1
Investigator CV	Charles Opondo_CV	03/08/2016	final
Advertisements	Recruitment procedures	29/08/2016	1
Safety Information	RUTF product characteristics v2	29/08/2016	2
Sponsor Letter	QA912_ComPAS Study	01/09/2016	1
Covering Letter	Cover letter_Response to LEO Stage 2_ 24 Oct 2016	24/10/2016	1
Information Sheet	Participant Info Sheet_Kenya_v3_24 Oct	24/10/2016	3
Information Sheet	Participant Info Sheet_South Sudan_v3_24 Oct	24/10/2016	3
Information Sheet	Health Facility Info Sheet_Kenya_v3_24 Oct	24/10/2016	3
Information Sheet	Health Facility Info Sheet_South Sudan_v3_24 Oct	24/10/2016	3
Information Sheet	Participant consent form_v3_24 Oct	24/10/2016	3
Information Sheet	Health facility consent form_v3_24 Oct	24/10/2016	3
Protocol / Proposal	ComPAS Study Protocol_Global_v3_24 Oct	24/10/2016	3

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

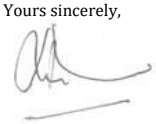
An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,



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E-mail: dlrector@kemrt.org, lnfo@kemrt.org, Webalte. www.kemrt.org

KEMRI/RES/7 /3/1 **January OS, 2017**

TO: **VIDDAH OWINO (PRINCIPAL INVESTIGATOR),**
viddah.owino@rescue.org
INTERNATIONAL RESCUE COMMITTEE {IRC)

DearSir,

RE: PROTOCOL NO. NON-KEMRI 551 *(RESUBMISSION OF INITIAL SUBMISSION):* COMBINED PROTOCOL FOR ACUTE MALNUTRITION STUDY (ComPAS),(*VERSION 2.0 DATED 1ST DECEMBER, 2016)*

Reference is made to your letter dated 1st December, 2016. The KEMRI/Sc!entific and Ethics Review Unit (SERU) acknowledges receipt of the revised study documents on 20th December, 2016.

This is to inform you that the Committee notes that the issues raised during the 2srti KEMRI/Ethics Review Committee (ERC) held on **15th November, 2016** have been adequately addressed.

Consequently, the study is granted approval for implementation effective this day, **5th January, 2017** for a period of one year. Please note that authorization to conduct this study will automatically expire on **January 4, 2018.** If you plan to continue data collection or analysis beyond this date, please submit an application for continuation approval to SERU by **24th November, 2017.**

You are required to submit any proposed changes to this study to SERU for review and the changes should not be initiated until written approval from SERU is received. Please note that any unanticipated problems resulting from the implementation of this study should be brought to the attention of SERU and you should advise SERU when the study is completed or discontinued.

You may embark on the study.

Yours faithfully,

Q(Jl(Ht ,i _

DR. EVANS AMUKOYE,
ACTING HEAD,
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT

The Republic of South Sudan

Ministry of Health

TO: Pamela Onyoo **Date: 21th Nov. 2016**

Action against Hunger

RESEARCH APPROVAL LETTER

Dear Onyoo,

SUBJECT: COMBINED PROTOCAL FOR ACUTE MALNUTRITION STUDY (ComPAS)

I am writing in response to the request for authorization of the study on **"Combined Protocol for Acute Malnutrition in Northern Bahr El Ghazal State"**

After close review on further clarifications and amendments to the proposal made, I am glad to inform you that the ethnical committee at the Ministry of Health for the Republic of South Sudan has approved the study. The Ministry acknowledges the importance of the study is to assess growth trends and energy requirement on acute Malnutrition in **Aweil East County**. Therefore, the members of the ethnical committee advise that this situation should be handled with great care, taking into consideration specific steps that minimize any risk, and counseling interventions.

Please, keep the Ministry informed in case of any changes regarding the study and on its progress. I look forward to the report, especially the recommendations that will be generated. Note that any information generated from the study should not be published without the consent of the Ministry.

Good luck and don't heisted to get in touch should there be any queries.

Dr. Richard L[redacted]
Director Gen[redacted]planning, budgeting and Research
Ministry of Health, Republic of South Sudan – Juba

CC: Undersecretary –MOH-RSS
CC: Director General, Primary Health Care –MOH-RSS
Cc: Director General State Ministry of Health - NBGS.

Headquarters, Ministerial Complex. Juba, South Sudan - P.O.Box 88, Juba.
Tel: +211 (0) 177 800 281 / +211 (0) 177 800 278

C: Consent form

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

PARTICIPANT CONSENT FORM

Title of Project: Combined Protocol for Acute Malnutrition Study (ComPAS)

Name of PI/Researcher responsible for project: Jeanette Bailey

Statement	**Please initial or thumbprint* each box**
I confirm that I have read the information sheet dated 24-October-16 (version 3) for the above named study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. **OR** I have had the information explained to by study personnel in a language that I understand. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from the London School of Hygiene and Tropical Medicine, International Rescue Committee and Action Against Hunger, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I agree to take part in the above named study	

Printed name of participant	Signature of participant	Date

Printed name of impartial witness*	Signature of impartial witness*	Date

I attest that I have explained the study information accurately in_____to, and was understood to the best of my knowledge by, the participant and that he/she has freely given their consent to participate* in the presence of the above named impartial witness (where applicable).

Printed name of person obtaining consent	Signature of person obtaining consent	Date

[*Only required if the participant is unable to read or write.]

A copy of this informed consent document has been provided to the participant.

Centre Number:
Study Number:
Participant Identification Number:

D: Data collection forms

Research Officer Name: _____

ComPAS ID: ☐☐☐☐

Form 1 Group A

ComPAS Kenya
Form 1: Admission Form

Instructions: The Research Officer will fill out this form for all children eligible for enrollment into the study.

Facility Name: _____

Date: ☐☐ ☐☐
DD **MM**

Child's Name: _____ _____
First Name Last Name

Section A: Biographic Information

			Please **circle** your response or enter integer
1.	**Child Information**	Do you know the child's exact date of birth?	(Circle one) Yes No→ go to 1c
	1a.	**Child Information** Enter Date of Birth	☐☐ ☐☐ ☐☐☐☐ DD MM YYYY
	1b.	**Child Information** What is the source of the date of birth?	(Circle one) Caregiver report Taken from documentation (example: MIYCN booklet) ➡ For both responses, go to 1d
	1c.	**Child Information** Enter child's age in months as reported by caregiver (min 6 months, max 59 months)	☐☐
	1d.	**Child Information** What is the child's sex?	(Circle one) Male Female

Research Officer Name: _____

ComPAS ID: ☐☐☐☐

Form 1 Group A

2.	**Admission Anthropometry**		Extract data from OTP / SFP patient card or register **Weight in kg :** (min 04.00, max 30.00) ☐☐ . ☐☐ **Height in cm:** (min 025.0, max 135.0) ☐☐☐ . ☐ **Weight-for-height z-score (check one):** ☐ ≥ -2z ☐ < -2z to ≥ -3z ☐ <-3z **MUAC in cm:**(min 06.0, max 16.0) ☐☐ . ☐
	2a.	**Does the child have oedema (+/++)?**	(Circle one) Yes No
	2b.	**Did child pass appetite test?**	(Circle one) Yes No→ STOP. Child is not eligible for study. This child will not be registered and should be referred to the SC.
	2c.	**Did clinician identify any medical complications requiring referral to SC?**	(Circle one) Yes→ STOP. Child is not eligible for the study and should be referred to the SC. No→ Child is eligible for the study.
3.	**Caregiver Information** Is respondent primary caregiver or responsible guardian?		(Circle one) Yes No → Child is not eligible for the study.
4.	**Consent Information** Did Research Officer go through the participant information sheet with caregiver?		(Circle one) Yes No→ STOP
	4a.	**Consent Information** Did caregiver agree to participate in the study and sign the consent form?	(Circle one) Yes → Proceed to section B No→ STOP

Research Officer Name: _____

ComPAS ID: | | | | |

Form 1 Group A

Section B: Admission Caregiver Questionnaire

			Please circle your response, enter text, or enter integer
1.	**Child Information** Give / Enter ComPAS registration number		| | | | |
2.	**Caregiver Information** What is the name of the primary caregiver?		First Name: _____ Last Name: _____
	2a.	**Caregiver information** What is your relationship to the child?	(Circle one) Mother Father Grandmother Sibling Other (please specify) _____
	2b.	**Caregiver Information** Primary caregiver's sex	(Circle one) Male Female
	2c.	**Caregiver's mobile number** (or other number where we can contact)	
	2d.	**Address of caregiver**	

Research Officer Name: _____

ComPAS ID: | | | | |

Form 1 Group A

3.	**Medical History** Does the child have an alive twin?		(Circle one) Yes No Don't know
	3a.	**Medical History** In the past week, has the child sought care from a medical clinic or health facility? This does not include the OTP or SFP	(Circle one) Yes No Don't know
	3b.	**Medical History - Diarrhea** In the past week, did the child suffer from diarrhea (have watery stool 3 or more times in one day)?	(Circle one) Yes No→ go to 3d Don't know→ go to 3d
	3c.	If yes, how many days has the child suffered from diarrhea in the past week?	☐ Enter days 1-7 Enter 9 if don't know
	3d.	**Medical History – Vomiting** In the past week, did the child suffer from vomiting?	(Circle one) Yes No→ go to 3f Don't know→ go to 3f
	3e.	If yes, how many days has the child suffered from vomiting in the past week?	☐ Enter days 1-7 Enter 9 if don't know
	3f.	**Medical History - Fever** In the past week, did the child suffer from fever?	(Circle one) Yes No→ go to 3h Don't know→ go to 3h

	3g.	If yes, how many days has the child suffered from fever in the past week?	☐ Enter days 1-7 Enter 9 if don't know
	3h.	**Medical History - Cough** In the past week, did the child suffer from cough?	(Circle one) Yes No→ go to 3j Don't know→ go to 3j
	3i.	If yes, how many days has the child suffered from cough in the past week?	☐ Enter days 1-7 Enter 9 if don't know
	3j.	**Medical History - Other** In the past week, did the child have any other illness? (e.g. malaria, pneumonia)	(Circle one) Yes No Don't know
	3k.	**Does the child have a physical or mental disability?**	(Circle one) Yes No Don't know
4.	**Breastfeeding information** If this child is <36 months, was this child ever breastfed?		(Circle one) Yes No→ go to 5 Child is older than 36 months→ go to 5 Don't know→ go to 5
	4a.	**Breastfeeding information** Was the child breastfed in the last 24 hours?	(Circle one) Yes No→ go to 5 Don't know→ go to 5

Research Officer Name: _____

ComPAS ID: | | | | |

Form 1 Group A

	4b.	**Breastfeeding information** How many times was the child breastfed in the last 24 hours?	☐☐ 0-20 times 99 if don't know
	4c.	**Breastfeeding information** Was this child fed any solid, semi-solid, or soft foods in the last 24 hours?	(Circle one) Yes No Don't know
5.		**Family Characteristics** For the past month, how many people have been living in this child's household?	☐☐ 0-20 99 if don't know
	5a.	**Family Characteristics** How many children under five years of age live in the child's household? (including the child)	☐☐ 0-20 99 if don't know
	5b.	**Family Characteristics** What is the highest level of the primary caregiver's education?	(Circle one) None Pre-primary Primary Secondary Don't know
6.		**Household Characteristics** What is the occupation of the main breadwinner in the child's household?	(Circle one) No income Sale of livestock Sale of crops Petty trading (e.g. sale of firewood, hawking) Casual labor (waged) Permanent job (salaried) Sale of personal assets Remittance

			Government assistance Business/shopkeeper Don't know Other (specify) _____
	6a.	**Household Characteristics** What is the household's primary source of drinking water?	(Circle one) Community tap Household tap Borehole (private) Vendors Don't know Other
	6b.	**Household Characteristics** Where does the household defecate most of the time?	(Circle one) Shared toilet Household toilet Community toilet Flying toilet Don't know Other (please specify) _____
7.	**Household Hunger** In the past 4 weeks or (30 days): Was there ever no food to eat of any kind in your house because of lack of resources to get food?		(Circle one) Never – 0 times Rarely – 1 to 2 times Sometimes – 3 to 10 times Often – greater than 10 times Don't know
	7a.	**Household Hunger** In the past 4 weeks or (30 days): Did you or any household member go to	(Circle one) Never – 0 times

		sleep at night hungry because there was not enough food?	Rarely – 1 to 2 times Sometimes – 3 to 10 times Often – greater than 10 times Don't know
	7b.	**Household Hunger** In the past 4 weeks or (30 days): Did you or any household member go a whole day and night without eating anything at all because there was not enough food?	(Circle one) Never – 0 times Rarely – 1 to 2 times Sometimes – 3 to 10 times Often – greater than 10 times Don't know
	7c.	**Household Hunger** In the past 4 weeks or (30 days): Has the household received food distribution from the government or NGOs?	(Circle one) Yes No Don't know

Research Officer Name: _____

ComPAS ID: | | | | |

Form 1 Group A

Section C: Admission Child Status Form

			Please **circle** your response, enter text, or enter integer
1.	**Admission Criteria for Combined Protocol Children** How was the child admitted?		**(Circle one)** Direct from community (CHV or self referral) From Stabilization Center (SC) Discharged from OTP (SAM child became MAM)
	1a.	What admission criteria did the child meet?	(Circle all that apply) Oedema (+/++) MUAC < 11.5 cm MUAC ≥ 11.5cm < 12.5cm WHZ score <-3 SD WHZ score <-2SD ≥ -3SD Other, please specify:_____
2.	**Medical History** Choose HIV status at time of admission		(Circle one) Negative Positive Exposed (biological mother is HIV positive) Unknown
	2a.	**Medical History** Choose TB status at time of admission	(Circle one) Negative Positive Unknown
3.	**Therapeutic Food** Number of RUTF sachets provided		| | | | Enter 00-14 sachets

END OF FORM
Provide caregiver the sachets and next return date.

Research Officer Name: _____

ComPAS ID: | | | | |

Form 2 Group A

ComPAS Kenya
Form 2: Follow-up Form

Instructions: The Research Officer will fill out this form for all children who are enrolled in the study and return for a follow-up visit. These forms will be filled out until the child exits the nutrition program.

Facility Name: _____

Date: | | | | **DD** **MM** **Visit week #:** | |

Child's Name: _____ _____
First Name Last Name

ComPAS ID: | | | | |

Section A: Caregiver questions

			Please **circle** your response, enter text, or enter integer
1.	**Caregiver information** What is your relationship to the child?		(Circle one) Mother Father Grandmother Sibling Other (please specify) _____
	1a.	**Caregiver information** Is the respondent a responsible caregiver or guardian of the child?	(Circle one) Yes No → Skip all remaining caregiver questions.
2.	**Breastfeeding information** If the child is <36 months, was the child breastfed in the last 24 hours?		(Choose one) Yes No→ go to 3 Don't know→ go to 3
	2a.	**Breastfeeding information** How many times was the child breastfed in the last 24 hours?	| | 0-20 times 99 if don't know

Research Officer Name: _____

ComPAS ID: | | | | |

Form 2 Group A

	2b.	**Breastfeeding information** Was this child fed any solid, semi-solid, or soft foods in the last 24 hours?	(Circle one) Yes No Don't know
3.	**Medical History** In the past week, has the child sought care from a medical clinic or health facility? This does not include the OTP or SFP.		(Circle one) Yes No Don't know
	3a.	**Medical History-Diarrhea** In the past week, did the child suffer from diarrhea (watery stool 3 or more times in one day)?	(Circle one) Yes No→ go to 3c Don't know→ go to 3c
	3b.	If yes, how many days has the child suffered from diarrhea?	(Enter days 1-7) ☐
	3c.	**Medical History-Vomiting** In the past week, did the child suffer from vomiting?	(Circle one) Yes No→ go to 3e Don't know→ go to 3e
	3d.	If yes, how many days has the child suffered from vomiting?	(Enter days 1-7) ☐
	3e.	**Medical History-Fever** In the past week, did the child suffer from fever?	(Circle one) Yes No→ go to 3g Don't know→ go to 3g
	3f.	If yes, how many days has the child suffered from fever?	(Enter days 1-7) ☐

Research Officer Name: _____

ComPAS ID: | | | | |

Form 2 Group A

	3g.	**Medical History-Cough** In the past week, did the child suffer from cough?	(Circle one) Yes No→ go to 3i Don't know→ go to 3i
	3h.	If yes, how many days has the child suffered from cough?	(Enter days 1-7) ☐
	3i.	**Medical History** In the past week, did the child have any other illness? (e.g. malaria, pneumonia)	(Circle one) Yes No Don't know
4.	**RUTF/RUSF Usage** Did the child have any problems eating the RUTF?		(Circle one) Yes No Don't know
	4a.	**RUTF Usage** How many sachets do you have remaining from the last distribution?	☐☐ 0-42 sachets → If 0, go to 4b, all other integers, go to 4c 99 if don't know
	4b.	**RUTF Usage** When were the sachets finished?	☐☐ ☐☐ **DD** **MM**
	4c.	**RUTF Usage** How many sachets were shared with other family members?	☐☐ 0-42 sachets 99 if don't know
5.	**Household Food Security** In the past month, has the household received food distribution from the government or NGOs?		(Circle one) Yes No Don't know

Research Officer Name: _____

ComPAS ID: ☐☐☐☐

Form 2 Group A

Section B: Child Status

			Please **circle** your response, enter text, or enter integer
1.	**Anthropometry**		**Weight in kg :** (min 04.00, max 30.00) ☐☐ . ☐☐ **Weight-for-height z-score (check one):** ☐ ≥ -2z ☐ < -2z to ≥ -3z ☐ <-3z **MUAC in cm:** (min 06.00, max 16.00) ☐☐ . ☐
	1a.	**Anthropometry** Was height taken this week?	(Circle one) Yes→ go to 1b No→ go to 1c
	1b.	**Anthropometry** Enter <u>height taken this week</u>.	Extract from OTP / SFP patient card or register **Height in cm:** (min 025.0, max 135.0) ☐☐☐ . ☐ → go to 1d
	1c.	**Anthropometry** Enter <u>most recent height recorded</u>.	Extract from OTP / SFP patient card or register **Height in cm:** (min 025.0, max 135.0) ☐☐☐ . ☐
	1d.	**Admission Anthropometry** Does the child have oedema (+/++)?	(Circle one) Yes No
2.	**Treatment Outcome for Combined Protocol** Is the MUAC measurement ≥ 12.5 cm?		(Circle one) Yes→ got to 2a No→ go to 2b
	2a.	**Treatment Outcome for Combined Protocol** Did the child have 2 consecutive visits with a MUAC ≥ 12.5cm?	(Circle one) Yes→ This child can now be discharged. Generate 4 month follow up date to give caregiver and begin Form 3-Caregiver Cost Questionnaire. No→ go to 2b

	2b.	**Treatment Outcome for Combined Protocol** What is the child's treatment outcome?	(Circle one) Child is still in treatment **Outcome attained**: cured from malnutrition **Outcome attained**: Non-Response **Outcome attained**: Referred Begin Form 3-Caregiver Cost Questionnaire If cured → provide 4 month follow-up date
3.	**Therapeutic Food for Combined Protocol** Total number of RUTF sachets provided		☐ 0-14 sachets

END OF FORM
Provide caregiver the sachets and next return date.

ComPAS Kenya
Form 3 – Caregiver Cost Questionnaire

Instructions: The Research Officer will fill out this form for every child who is enrolled in our study and is being discharged from the program.

Facility Name:_____ **Research Officer Name:** _____

Date: ☐☐ ☐☐ **Visit week #:** ☐☐
DD MM

Child's Name: _____ _____
First Name Last Name

ComPAS ID: ☐☐☐☐

1.	**What is the name of the village/neighborhood/block you are coming from?**	Enter Text:_____
2.	**How did you come to the health facility today?**	(Circle one) Walking Motorbike (own) Motorbike (hired) Matatu Personal transport Other (specify_____)
3.	**How long did it take you to get here (from the time you left your house until you arrived at the facility)?**	(circle one) <30 minutes 30-59 minutes 1 - <2 hours 2- <4 hours ≥ 4 hours
4.	**How much did it cost for transportation to get to the health facility today (one way)? Estimate cost of fuel if your own transport or cost of hire.**	(Enter KSH) ☐☐☐☐ Write "0000" if they walked

5.	**How will you return home today?**	(Circle one) Walking Motorbike (own) Motorbike (hired) Matatu Personal transport Other (specify_____)
6.	**How long will it take you to return home (from the time you leave the facility until you arrive at home)?**	(circle one) <30 minutes 30-59 minutes 1 - <2 hours 2- <4 hours ≥ 4 hours
4.	**How much will it cost for transportation to get home today (one way)? Estimate cost of fuel if your own transport or cost of hire.**	(Enter KSH) [ ][ ][ ][ ] Write "0000" if they walked

END OF FORM - The child is now discharged from the treatment program.

E: Supplementary materials for Paper I

Procedures for taking anthropometric measurements

Protocol for taking weight measurements:

The child's weight will be measured and documented at admission as well as at each follow-up visit.

1. Record weight using the ComPAS-designated SECA 385 scale, only
2. Ensure scale is on level floor or table top and set to zero (baby tray can be removed for children who are able to stand on their own)
3. Press 'start' button for first use or 'reset' button between each measurement; wait for '00.0000' to appear
4. Child removes any shoes and heavy clothing
5. Child is placed on tray or child stands on center of the scale, sitting/standing still (caregiver or clinician may have to persuade child to remain calm)
6. Clinician records measurement once reading is stable (digits will flash once and then stabilize)
7. Measurement is recorded to the nearest 0.01kg

Protocol for taking height/length measurements:

The child's height/length will be measured and documented at admission as well as on a monthly basis thereafter. Length is measured for those aged <2, height for those ≥2 years. This measurement will be taken by two operators, and measurements compared.

1. Child should remove shoes and any hair ornaments that may interfere with reading
2. Child is laid or stands straight with heels against height/length board, toes directly in the air (feet at 90°angle standing position) or feet flat on floor
3. Ensure back, shoulders, head, buttocks are flat against height board and heels are flat against heel plate
4. Ensure the head in line with neck and shoulders (chin level)
5. Clinician moves foot board against child's feet or head board onto child's head
6. Clinician places hands under the subjects ears to assist with posture and then asks child to breath in and then relax but stay tall
7. Measurement is recorded to the nearest 0.1cm
8. The two measurements should be within 0.5cm of each other. If they are not, both operators should repeat the measurements. If they are within 0.5cm of each other, the final value should be mid-way between the two (ie. added together and divided by 2)

Protocol for taking MUAC measurements:

The child's mid upper arm circumference will be measured and documented at admission to determine eligibility for treatment as well as at each follow-up visit.

1. Shirt should be removed
2. Take the left arm of the child
3. Place the left arm of the child across his chest and ask the caregiver to keep the arm in this position.
4. Use the MUAC tool to determine the mid-point between the shoulder and tip (bone) of elbow
5. Strap the MUAC tool around the arm of the child at the identified mid-point, be sure tape is level and tension is correct (no skin bulging from the top or bottom of the MUAC tape)
6. With the arm of the child hanging down, record the digits that are shown at the arrow in the hole of the MUAC tool (round to the nearest 1 mm).
7. When recording on the form, use two digits to the left of the decimal place, and one digit to the right.

Protocol for checking for oedema:

A condition of bilateral pitting oedema (level + or ++) meets the criteria for admission into the study. Do not force the appearance of a pit by pushing too hard, especially with a fingernail. It is not accurate to report nutritional oedema if only one foot has oedema. Oedema level +++ should be immediately referred for inpatient care.

1. While child's foot is limp, press firmly with the pad (not tip) of thumb on the top of the child's feet for 5 seconds, then release
2. Check each for a pit or indentation that lasts as least 2 seconds after release

F: Supplementary materials for Paper III

Supplemental materials to accompany "A simplified, combined protocol versus standard treatment for acute malnutrition (ComPAS trial): a cluster randomized controlled non-inferiority trial"

Supplemental table 1: Comparison of Combined and Standard Protocols

	Standard Protocol (CONTROL)	**Combined Protocol (INTERVENTION)**
Eligibility criteria	Age 6-59 months, MUAC <12·5cm and/or edema (+/++), and clinically uncomplicated (i.e. passes appetite test, no Integrated Management of Childhood Illness (IMCI) danger signs/ no serious medical complications)	Age 6-59 months, MUAC <12·5cm and/or edema (+/++), and clinically uncomplicated (i.e. passes appetite test, no Integrated Management of Childhood Illness (IMCI) danger signs/ no serious medical complications)
Admission criteria	**OTP** • WHZ < -3 AND/OR • MUAC < 115mm AND/OR • Bilateral pitting edema (+/++) AND • clinically uncomplicated **SFP** • Discharged from OTP AND/OR • WHZ <-2 to WHZ >-3 AND/OR • MUAC 115mm- < 125mm AND • clinically uncomplicated	• <125mm MUAC AND/OR • Bilateral pitting edema (+/++) AND • clinically uncomplicated
Treatment frequency	**OTP** Weekly **SFP** 14 days	**MUAC <115mm and/or edema (+/++)** Weekly **MUAC 115-<125mm** 14 days
Treatment transition criteria	• Child meets OTP 'cured' definition as described below	• Two consecutive MUAC measurements at or above 115mm AND • No edema
Dosage	**OTP** RUTF 200kcal/kg/day **SFP** RUSF 500 kcal/day (1 sachet/day)	**MUAC <115mm and/or edema (+/++)** RUTF 1000 kcal/day (2 sachets/day) **MUAC 115-<125mm** RUTF 500 kcal/day (1 sachet/day)
Cured	**OTP** • Child maintains MUAC ≥115mm for two consecutive visits** AND/OR • WHZ >-3 Z-score for two consecutive visits** AND • No edema for two consecutive visits **SFP** Child maintains WHZ >-2 Z-score and/or MUAC ≥125mm for a period of two consecutive visits**	≥125mm for 2 consecutive measurements and no edema

Supplemental table 2: Admission characteristics of children by country

Characteristic	Kenya (n=1,988)	South Sudan (n=2,122)
Sex and age		
Males, n (%)	742 (37%)	940 (44%)
Age in months, mean (SD)	12·0 (7·0)	21·7 (12·0)
Age categories, n (%)		
6-<24 months	1,880 (94·6%)	1,164 (54·9%)
≥ 24 months	105 (5·3%)	954 (45·0%)
Anthropometrics		
Weight (kg), mean (SD)	6·8 (1)	7·7 (2)
Height (cm), mean (SD)	69·5 (6)	76·2 (10)
MUAC (cm), mean (SD)	11·8 (·5)	11·6 (·6)
WHZ, mean (SD)	-2·1 (1·0)	-2·7 (3·3)
HAZ, mean (SD)	-1·7 (1·5)	-2·3 (1·6)
WAZ, mean (SD)	-2·5 (1·0)	-3·2 (1·0)
MUAC <11·5cm, n (%)	354 (18%)	881 (42%)
and WHZ ≥-3 to <-2	123 (35%)	274 (31%)
and WHZ <-3	160 (45%)	538 (61%)
and WHZ >=-2	71(20%)	69(8%)
MUAC 11·5-<12·5cm, n (%)	1,631(82%)	1,227 (58%)
and WHZ ≥-3 to <-2	586 (36%)	614 (50%)
and WHZ <-3	173 (11%)	243 (20%)
and WHZ >=-2	872(54%)	370(30%)
Edema (+ or ++), n (%)	18 (1%)	29 (1%)
Household and other characteristics		
Mother is caretaker, n (%)	1,915 (96%)	1,986 (94%)
Maternal educational achievement, n(%)		
None	29(2%)	1735(87%)
Pre-primary	22(1%)	0(0%)
Primary	726(38%)	234(12%)
Secondary	1135(59%)	16(1%)
College tertiary	0(0%)	1(0%)
Number of children under five in the home, mean (SD)	1·1 (·7)	2·1 (·8)
Children breast fed in last 24 hours, n(%)	1,636 (82%)	1,227 (58%)
Caretaker reports any morbidity in past week*, n (%)	870 (44%)	1,629 (77%)
Fever	337 (17%)	1,164 (55%)
Diarrhea	275 (14%)	763 (36%)
Cough	479 (24%)	866 (41%)
Healthcare sought in prior week	367(19%)	521(25%)
HIV Status		
+	14(1%)	0(0%)
Exposed (Mother)	36(2%)	0(0%)
Disabled (physically or mentally)	29(2%)	53(3%)
Tuberculosis (+), n(%)	9(1%)	0(0%)
Access to toilet	1978(100%)	678(32%)
Water source		
Household tap	266 (13%)	0(0%)
Community tap/ tap stand	1381(70%)	45(2%)
Hand pump/ borehole	0(0%)	1264(60%)
Borehole (private)	26 (1%)	588(28%)
Vendors	304(15%)	0(0%)
Open water	1(0%)	218(10%)
Livelihood/ main source of income		
No income	121(6%)	1(0%)
Sale of items (grass, firewood, livestock)	81(4%)	340(16%)
Fishing/ farming	0(0%)	1208(57%)
Business/ shopkeeper	821(41%)	93(4%)
Casual labor	425(21%)	294(14%)
Salaried work	31(2%)	160(8%)
Other	6(0%)	19(1%)
Household Hunger Score		
Ever no food to eat?		
Never	1541(78%)	775(37%)

Rarely	286(14%)	653(31%)
Sometimes	126(6%)	590(28%)
Often	23(1%)	93(4%)
Don't know	2(0%)	7(0%)
Ever go to sleep without enough food?		
Never	1560(79%)	654(31%)
Rarely	280(14%)	753(36%)
Sometimes	114(6%)	631(30%)
Often	21(1%)	61(3%)
Don't know	3(0%)	19(1%)
Any HH member go whole day without eating anything?		
Never	1581(80%)	754(36%)
Rarely	257(13%)	688(32%)
Sometimes	122(6%)	578(27%)
Often	16(1%)	64(3%)
Don't know	2(0%)	34(2%)

Supplemental table 3: Coverage survey results by country, arm and SAM/MAM status

	Standard Protocol		Combined Protocol	
	SAM	**MAM**	**SAM**	**MAM**
Kenya (%) (95% CI)	52·9% (39·1% - 66·2%)	47·3% (37·1% - 58·0%)	54·9% (41·2% - 68·0%)	48·6% (38·0% - 59·4%)
South Sudan (%) (95% CI)	62·5% (47·8-75%)	26·3% (19·2-35·1%)	45·9% (32·5-59·9%)	21·3% (14·9-29·2%)

Definition of SAM: MUAC<11·5cm and/or edema (+/++); definition of MAM: MUAC 11·5-<12·5cm and no edema

Supplemental table 4: Analyses of recovery and length of stay by sub-group

Per Protocol Analysis	**Standard Protocol (N=12, n=1,202)**		**Combined Protocol (N=12, n=1,286)**		**Unadjusted**		**Adjusted**	
	n	**%**	**N**	**%**	**Risk difference[§] (95% CI)**	**p-value**	**Risk difference[§] (95% CI)**	**p-value**
Recovery among sub-groups by admission status								
SAM	111/294	37·8%	121/291	41·6%	0·04 (-0·06-0·13)	0·43	0·03 (-0·05-0·12)	0·42
MAM	773/ 908	85·1%	860/995	86·4%	0·01 (-0·07-0·10)	0·77	0·00 (-0·07-0·07)	0·97
Age <24 months	654/930	70·3%	667/928	71·9%	0·02 (-0·08- 0·11)	0·75	0·02 (-0·07-0 ·11)	0·62
Age ≥24 months	230/272	84·6%	314/358	87·7%	0·03 (-0·06-0·13)	0·52	0·04 (-0·06-0·13)	0·46
SAM & ≥8kg	29/54	53·7%	28/42	66·7%	0·13 (-0·08-0·34)	0·23	0·08 (-0·14-0·31)	0·47
MUAC 11·5-<12·5cm and WHZ<-3z	84/111	75·7%	134/190	70·5%	-0·05 (-0·19-0·08)	0·46	-0·05 (-0·16-0·07)	0·44
Kenya	516/686	75·2%	458/627	73·1%	-0·02 (-0·13-0·09)	0·71	-0·02 (-0·13-0·09)	0·70
South Sudan	368/516	71·3%	523/659	79·4%	0·08 (-0·03- 0·19)	0·16	0·08 (-0·02-0·18)	0·13
	Standard Protocol (N=12, n=1,201)		**Combined Protocol (N=12, n=1,286)**		**Unadjusted**		**Adjusted**	
	Mean	**SE**	**Mean**	**SE**	**Mean difference[§] (95% CI)**	**p-value**	**Mean difference[§] (95% CI)**	**p-value**
Length of stay by country								
Kenya	58·9	2·36	63·5	2·35	4·62 (-2·35-11·59)	0·17	4·73 (-2·07-11·52)	0·15
South Sudan	73·5	2·52	67·0	2·38	-6·45 (-13·53-0·63)	0·07	-6·37 (-13·17- 0·43)	0·06

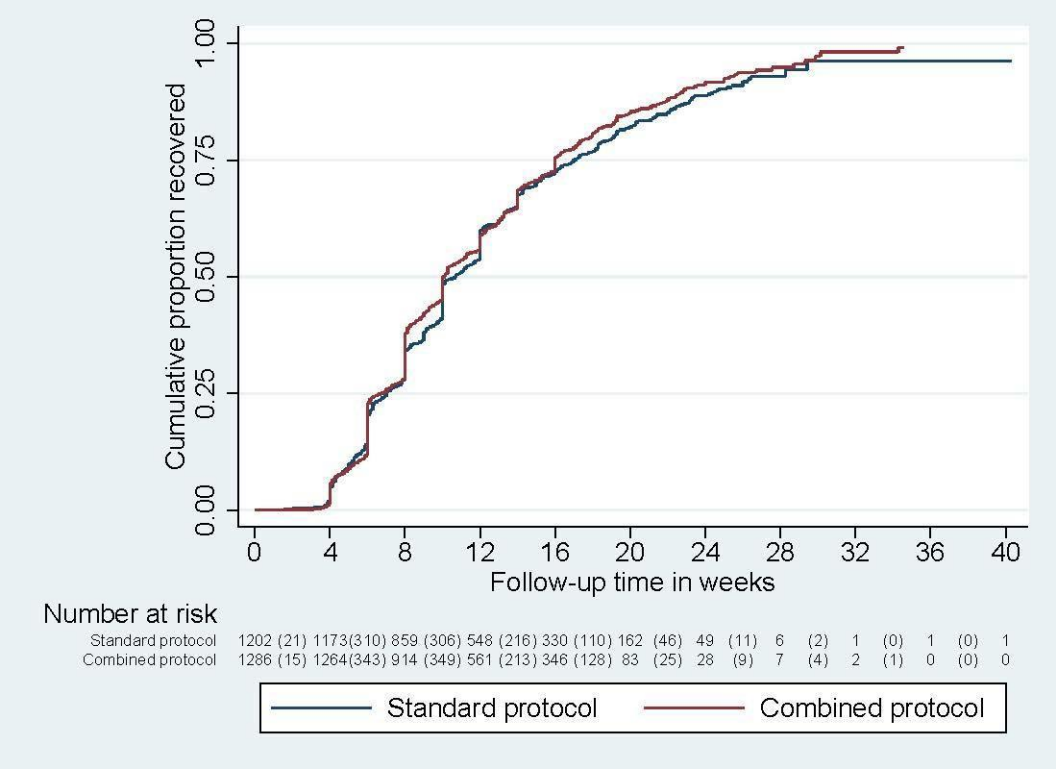
Unadjusted: All children with outcome measures, not adjusted for any demographic or study design characteristics; **Adjusted**: for age, sex and country; **N**= number of clusters; **n**=number of children eligible for follow up; [§]standard errors adjusted for clustering within facilities

Supplemental table 5: RUTF Dosage Table (based on 200 kcal/kg/day using 92g packets containing 500 kcal)

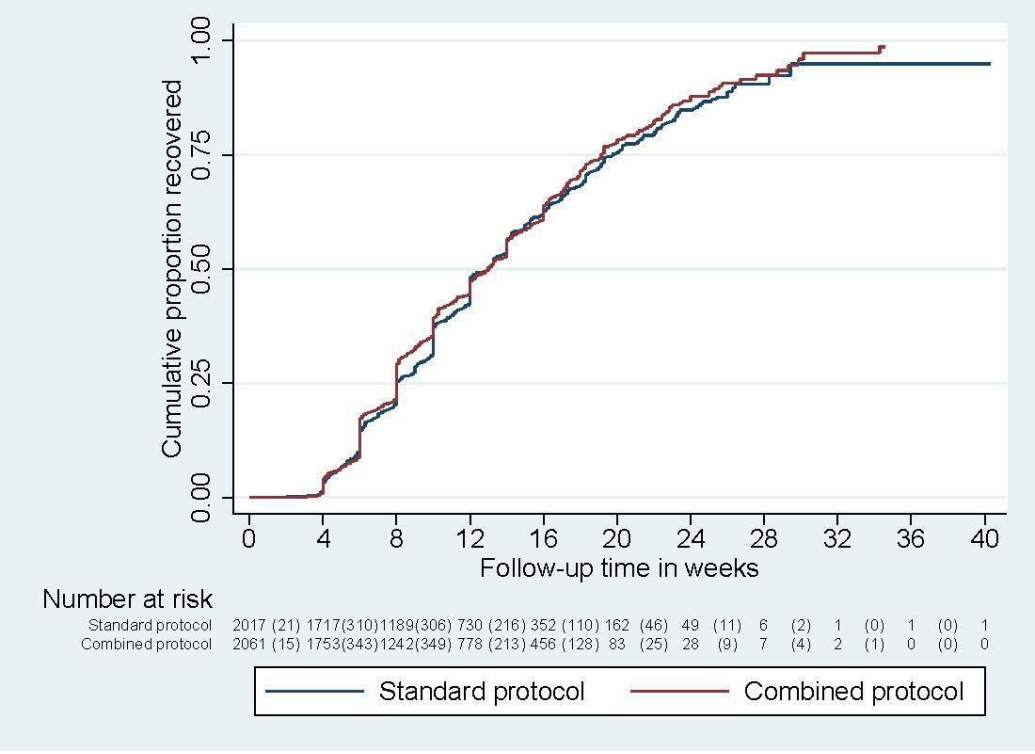
Child's weight (kg)	**Packets per day**	**Packets per week**
4·0*-4·9	2	14
5·0-6·.9	2·.5	18
7·0-8·4	3	21
8·5-9·4	3·.5	25
9·5-10·.4	4	28
10·5-11·.9	4·5	32
≥12	5	35

*Infants≥6 months and <4kg are referred to in-patient care

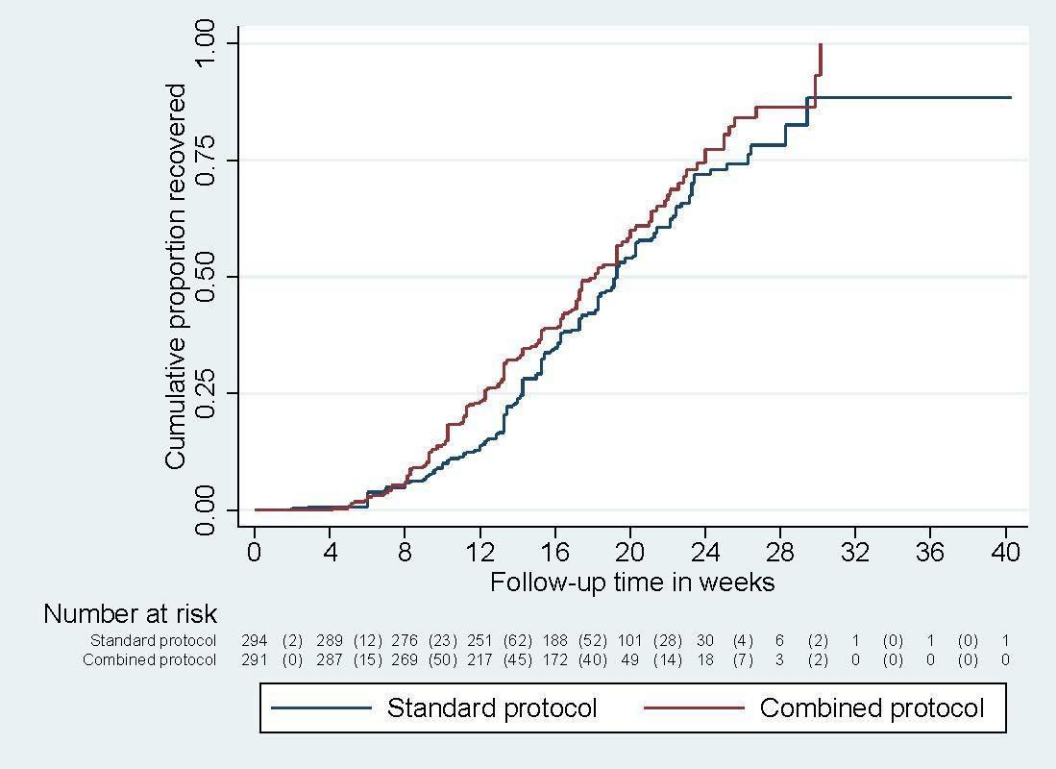
Supplemental figure 1: Time to recovery for all children in per-protocol analysis



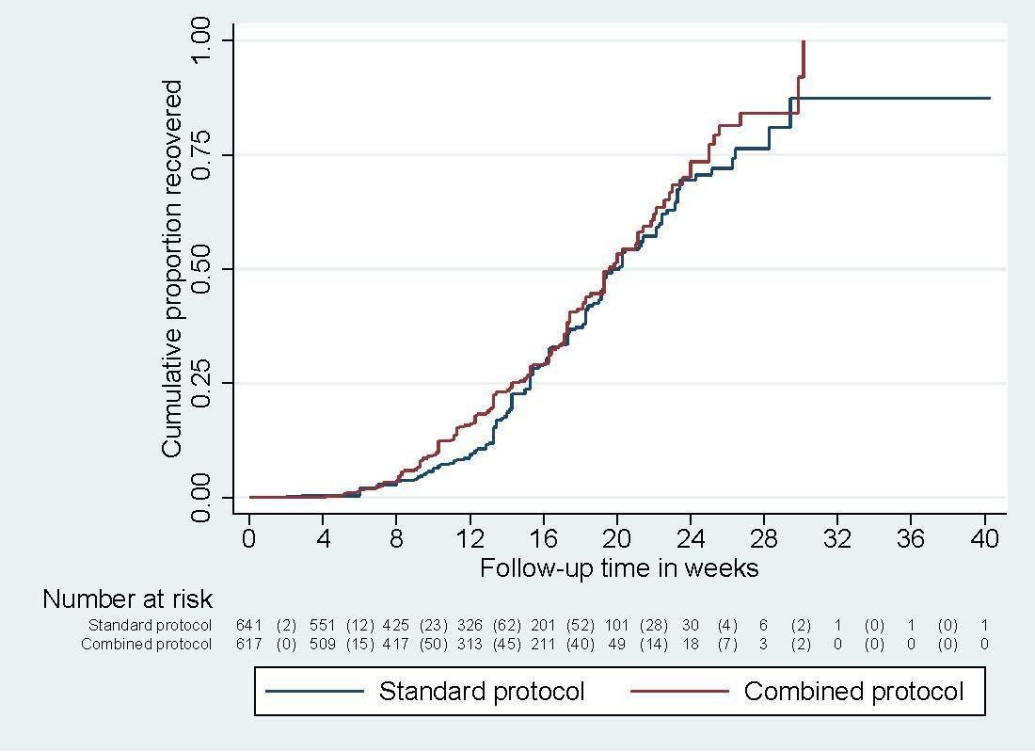
Supplemental figure 2: Time to recovery for all children in intention-to-treat analysis



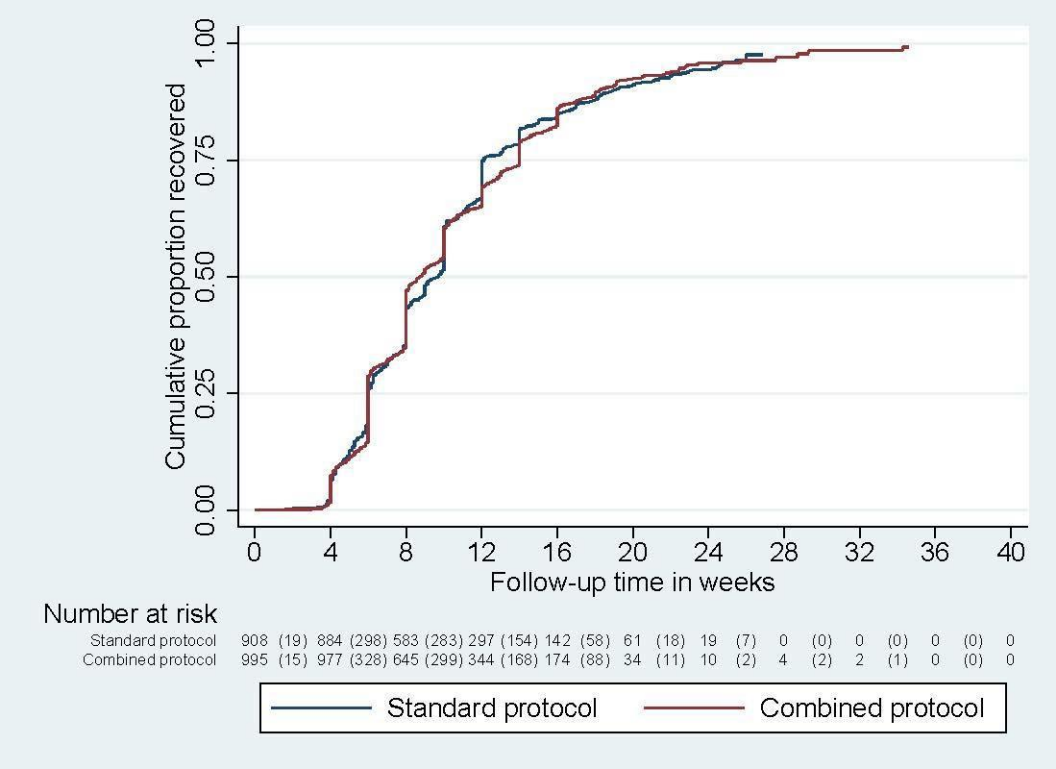
Supplemental figure 3: Time to recovery for SAM children in per-protocol analysis



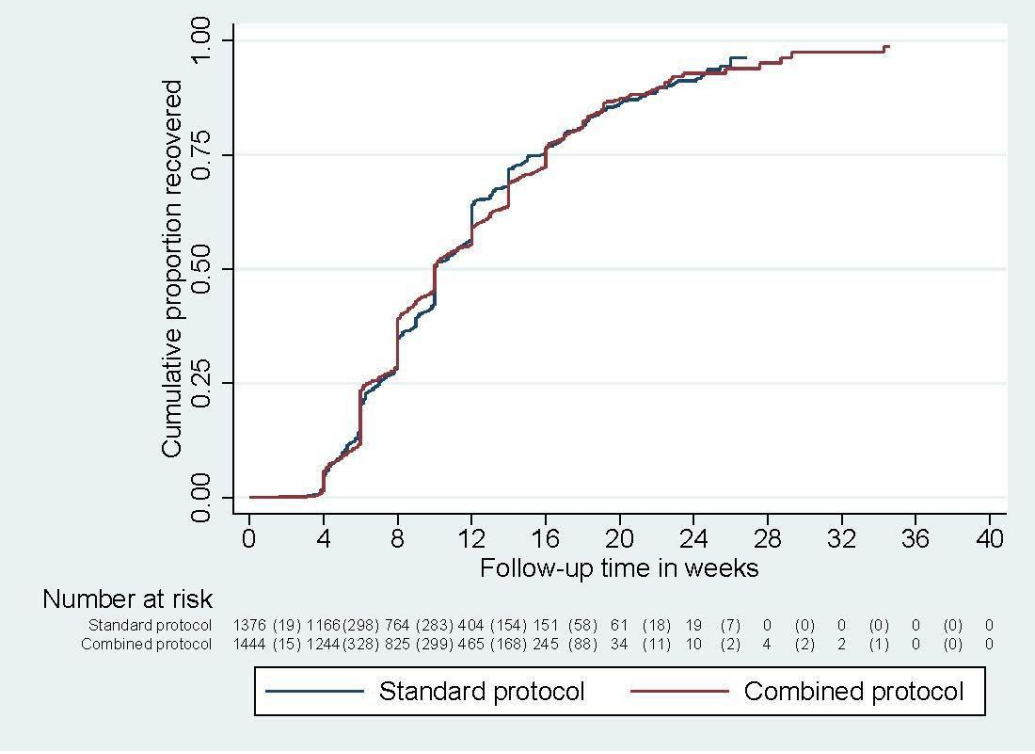
Supplemental figure 4: Time to recovery for SAM children in intention-to-treat analysis



Supplemental figure 5: Time to recovery for MAM children in per-protocol analysis



Supplemental figure 6: Time to recovery for MAM children in intention-to-treat analysis



Supplemental document 1: Procedures for taking anthropometric measurements

Protocol for taking weight measurements:

The child's weight will be measured and documented at admission as well as at each follow-up visit.

1. Record weight using the ComPAS-designated SECA 385 scale, only
2. Ensure scale is on level floor or table top and set to zero (baby tray can be removed for children who are able to stand on their own)
3. Press 'start' button for first use or 'reset' button between each measurement; wait for '00·0000' to appear
4. Child removes any shoes and heavy clothing
5. Child is placed on tray or child stands on center of the scale, sitting/standing still (caregiver or clinician may have to persuade child to remain calm)
6. Clinician records measurement once reading is stable (digits will flash once and then stabilize)
7. Measurement is recorded to the nearest 0·01kg

Protocol for taking height/length measurements:

The child's height/length will be measured and documented at admission as well as on a monthly basis thereafter· Length is measured for those aged <2, height for those ≥2 years This measurement will be taken by two operators, and measurements compared.

1. Child should remove shoes and any hair ornaments that may interfere with reading
2. Child is laid or stands straight with heels against height/length board, toes directly in the air (feet at 90°angle standing position) or feet flat on floor
3. Ensure back, shoulders, head, buttocks are flat against height board and heels are flat against heel plate
4. Ensure the head in line with neck and shoulders (chin level)
5. Clinician moves foot board against child's feet or head board onto child's head
6. Clinician places hands under the subjects ears to assist with posture and then asks child to breath in and then relax but stay tall
7. Measurement is recorded to the nearest 0·1cm
8. The two measurements should be within 0·5cm of each other. If they are not, both operators should repeat the measurements. If they are within 0·5cm of each other, the final value should be mid-way between the two (ie. added together and divided by 2)

Protocol for taking MUAC measurements:

The child's mid upper arm circumference will be measured and documented at admission to determine eligibility for treatment as well as at each follow-up visit.

1. Shirt should be removed
2. Take the left arm of the child
3. Place the left arm of the child across his chest and ask the caregiver to keep the arm in this position.
4. Use the MUAC tool to determine the mid-point between the shoulder and tip (bone) of elbow
5. Strap the MUAC tool around the arm of the child at the identified mid-point, be sure tape is level and tension is correct (no skin bulging from the top or bottom of the MUAC tape)
6. With the arm of the child hanging down, record the digits that are shown at the arrow in the hole of the MUAC tool (round to the nearest 1 mm).
7. When recording on the form, use two digits to the left of the decimal place, and one digit to the right.

Protocol for checking for oedema:

A condition of bilateral pitting oedema (level + or ++) meets the criteria for admission into the study. Do not force the appearance of a pit by pushing too hard, especially with a fingernail. It is not accurate to report nutritional oedema if only one foot has oedema. Oedema level +++ should be immediately referred for inpatient care.

1. While child's foot is limp, press firmly with the pad (not tip) of thumb on the top of the child's feet for 5 seconds, then release
2. Check each for a pit or indentation that lasts as least 2 seconds after release

G: Supplementary materials for Paper IV

Supplementary Table S1. Comparison of Combined and Standard Protocols *

	Standard Protocol (CONTROL)	Combined Protocol (INTERVENTION)
Eligibility criteria	Age 6–59 months, MUAC < 12.5 cm and/or oedema (+/++), and clinically uncomplicated (i.e., passes appetite test, no Integrated Management of Childhood Illness (IMCI †)**Error! Bookmark not defined.** danger signs/ no serious medical complications)	Age 6–59 months, MUAC <12.5cm and/or oedema (+/++), and clinically uncomplicated (i.e., passes appetite test, no Integrated Management of Childhood Illness (IMCI) danger signs/ no serious medical complications)
Admission criteria	**OTP** • WHZ < −3 AND/OR • MUAC < 11.5 cm AND/OR • Bilateral pitting oedema (+/++) AND • clinically uncomplicated **SFP** • Discharged from OTP AND/OR • WHZ < −2.0 to WHZ > −3 AND/OR • MUAC ≥ 11.5 cm and < 12.5 cm AND • clinically uncomplicated	• <12.5 cm MUAC AND/OR • Bilateral pitting oedema (+/++) AND • clinically uncomplicated
Treatment frequency	**OTP** Weekly **SFP** 14 days	**MUAC <11.5 cm and/or edema (+/++)** Weekly **MUAC ≥ 11.5 and < 12.5cm** 14 days
Treatment transition criteria	• Child meets OTP 'recovered' definition as described below	• Two consecutive MUAC measurements at or above 11.5 cm AND • No edema
Dosage	**OTP** RUTF 200 kcal/kg/day **SFP** RUSF 500 kcal/day (1 sachet/day)	**MUAC < 11.5 cm and/or edema (+/++)** RUTF 1000 kcal/day (2 sachets/day) **MUAC ≥ 11.5 and < 12.5 cm** RUTF 500 kcal/day (1 sachet/day)
Recovered	**OTP** • Child maintains MUAC ≥ 11.5 cm for two consecutive visits AND/OR • WHZ > −3 z-score for two consecutive visits AND • No edema for two consecutive visits **SFP** Child maintains WHZ > −2.0 z-score and/or MUAC ≥ 12.5 cm for a period of two consecutive visits	≥ 12.5 cm for 2 consecutive measurements and no edema

MUAC, mid-upper arm circumference; IMCI, Integrated Management of Childhood Illness; WHZ, weight-for-height z-score; OTP, outpatient therapeutic program; SFP, supplementary feeding program; RUTF, ready-to-use therapeutic food; RUSF, ready-to-use supplementary food. * Adapted from Bailey et al. 2018 [27] and Bailey et al. 2020 [35]. † Integrated Management of Childhood Illness (IMCI) (revised). 2014. http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/ (accessed on 22 March 2021).

Supplementary Table S2. Standard ready-to-use therapeutic food dosage table (based on 200 kcal/kg/day using 92 g packets containing 500 kcal) *

Child's Weight (kg)	Packets per Day	Packets per Week
4.0 †–4.9	2	14
5.0–6.9	2.5	18
7.0–8.4	3	21
8.5–9.4	3.5	25
9.5–10.4	4	28
10.5–11.9	4.5	32
≥12	5	35

* Adapted from Bailey et al 2020 [35]. † Infants ≥ 6 months and < 4kg are referred to in-patient care.

Supplementary Table S3. Relapse, body composition and morbidity at four months post-discharge, by admission category and protocol type (Kenya sample only)

Intention-to-Treat	**Group 1** MUAC < 11.5 cm and WAZ ≥ −3.0 (*n* = 29)				**Group 2** MUAC 11.5 to < 12.5 cm and WAZ < −3.0 (*n* = 140)				**Group 3** MUAC < 11.5 cm and WAZ < −3.0 (*n* = 56)			
	Combined (*N* = 6, *n* = 10)		**Standard** (*N* = 6, *n* = 19)		**Combined** (*N* = 6, *n* = 87)		**Standard** (*N* = 6, *n* = 53)		**Combined** (*N* = 6, *n* = 30)		**Standard** (*N* = 6, *n* = 26)	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Acute malnutrition status †	2	20	5	26	15	17	10	19	7	23	5	19
Relapse to acute malnutrition ‡)	1/4	25	1/10	10	10/68	15	6/35	17	1/12	8	1/13	8
Illness reported in past week §	2	20	9	47	21	24	12	23	6	20	8	31
Hospitalization reported in past 4 months	0	0	1	5	5	6	3	6	1	3	2	8
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Fat free mass (kg)	6.29	0.54	6.26	0.62	6.08	0.82	6.22	0.88	6.18	0.66	6.16	0.70
Fat mass (kg)	2.26	0.61	2.43	0.63	2.15	0.84	2.31	0.93	2.44	1.14	2.10	0.77

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score. *N* = number of clusters; *n* = individual children eligible for treatment. † At 4-month follow-up visit. ‡ Among those discharged as cured. § Data collected on reported diarrhea, vomiting, fever or cough in past week.

Supplementary Table S4. Outcomes of children in group 1, unadjusted and adjusted risk ratios

Intention-to-Treat	Group 1 MUAC < 11.5 cm and WAZ ≥ −3.0 (*n* = 337)							
	Combined (*N* = 12, *n* = 142)		Standard (*N* = 12, *n* = 195)		Unadjusted Risk Ratio †		Adjusted Risk Ratio †	
	n	%	n	%	Risk ratio (95% CI)	*p*-Value ‡	Risk ratio (95% CI)	*p*-Value ‡
Recovered	25	17.6	41	21.0	0.84 (0.52, 1.35)	0.47	0.87 (0.54, 1.40)	0.56
Died	1	0.7	2	1.0	0.69 (0.07, 6.45)	0.74	0.57 (0.05, 6.55)	0.65
Defaulted	48	33.8	83	42.6	0.79 (0.57, 1.11)	0.18	0.81 (0.58, 1.12)	0.20
Non-recovered §	46	32.4	56	28.7	1.13 (0.75, 1.70)	0.57	1.16 (0.77, 1.74)	0.48
Transfer-inpatient	7	4.9	2	1.0	3.20 (0.68, 15.04)	0.14	3.13 (0.76–12.96)	0.12
Transfer-new facility	6	4.2	2	1.0	4.12 (0.74, 22.87)	0.11	4.08 (0.75, 22.13)	0.10
Early discharge	9	6.3	9	4.6	1.53 (0.61, 3.80)	0.36	1.54 (0.68, 3.45)	0.30
	Median	**IQR**	**Median**	**IQR**	**Common Language Effect Size statistic (control > intervention) * (95% CI)**			
Length of stay (days) [a]	80	59, 94	94	85, 108	0.63 (0.49, 0.78)			

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score. *N* = number of clusters; *n* = individual children eligible for treatment. † Both unadjusted and adjusted results account for the effect of clustering. The adjusted model also includes adjustment for country, age and sex. ‡ Analyses use the Generalized Linear Model, reporting Pearson chi-squared *p*-values. § Non-recovered defined as not reaching recovery criteria after 17 weeks in treatment. [a] Length of stay among recovered children only, per global CMAM reporting standards [46]. * Probability that a randomly selected control length of stay is greater than a randomly selected intervention length of stay.

Supplementary Table S5. Outcomes of children in group 2, unadjusted and adjusted risk ratios

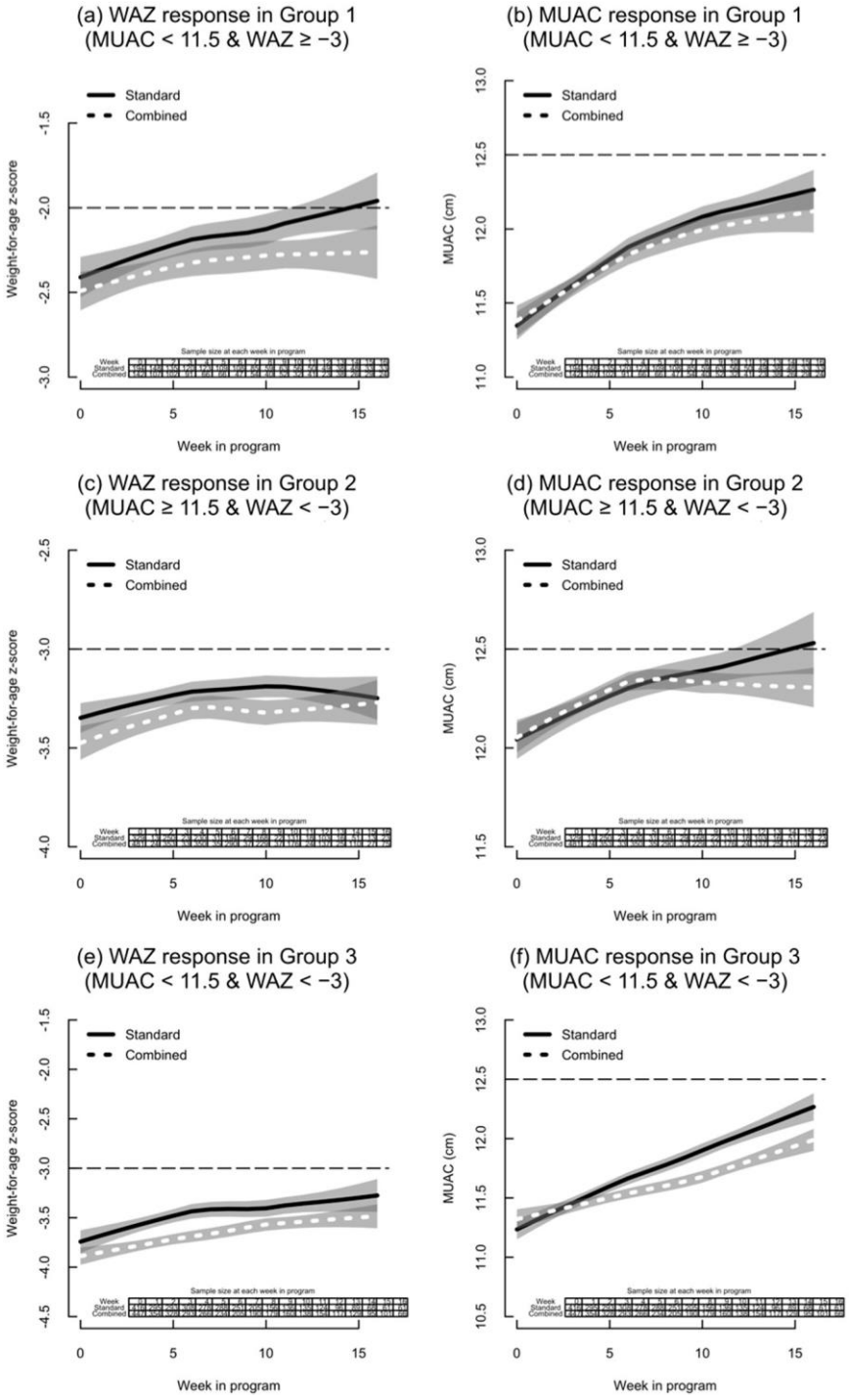
Intention-to-Treat	Group 2 MUAC 11.5 to <12.5cm and WAZ < −3.0 (n=811)							
	Combined (*N* = 12, *n* = 482)		Standard (*N* = 12, *n* = 329)		Unadjusted Risk Ratio †		Adjusted Risk Ratio †	
	n	%	*n*	%	Risk Ratio (95% CI)	*p*-Value ‡	Risk Ratio (95% CI)	*p*-Value ‡
Recovered	274	56.9	163	49.5	1.15 (0.85, 1.55)	0.37	1.18 (0.90, 1.54)	0.24
Died	4	0.83	3	0.91	0.91 (0.16, 5.25)	0.92	0.75 (0.15, 3.86)	0.73
Defaulted	92	19.1	79	24.0	0.78 (0.45, 1.37)	0.39	0.78 (0.51, 1.19)	0.25
Non-recovered §	41	8.5	28	8.5	1.0 (0.40, 2.50)	1.0	0.82 (0.41, 1.63)	0.58
Transfer-inpatient	5	1.0	5	1.5	0.68 (0.13, 3.59)	0.65	0.68 (0.14, 3.28)	0.63
Transfer-new facility	9	1.9	6	1.8	0.98 (0.37, 2.60)	0.96	1.06 (0.45, 2.48)	0.90
Early discharge	57	11.8	45	13.7	0.89 (0.46, 1.72)	0.73	0.95 (0.57, 1.61)	0.86
	Median	**IQR**	**Median**	**IQR**	**Common Language Effect Size Statistic (control > intervention) * (95% CI)**			
Length of stay (days) [a]	57	43, 85	71	57, 85	0.52 (0.46, 0.58)			

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score. *N* = number of clusters; *n* = individual children eligible for treatment. † Both unadjusted and adjusted results account for the effect of clustering. The adjusted model also includes adjustment for country, age and sex. ‡ Analyses use the Generalized Linear Model, reporting Pearson chi-squared *p*-Values. § Non-recovered defined as not reaching recovery criteria after 17 weeks in treatment. [a] Length of stay among recovered children only, per global CMAM reporting standards [46]. *Probability that a randomly selected control length of stay is greater than a randomly selected intervention length of stay.

Supplementary Table S6. Outcomes of children in group 3, unadjusted and adjusted risk ratios

Intention-to-Treat	Group 3 MUAC < 11.5 cm and WAZ < –3.0 (*n* = 863)							
	Combined (*N* = 12, *n* = 447)		Standard (*N* = 12, *n* = 416)		Unadjusted Risk Ratio †		Adjusted Risk Ratio †	
	n	%	*n*	%	Risk ratio (95% CI)	*p*-Value ‡	Risk ratio (95% CI)	*p*-Value ‡
Recovered	87	19.5	57	13.7	1.42 (0.89, 1.95)	0.06	1.36 (0.90, 1.82)	0.07
Died	9	2.0	7	1.7	1.20 (0.30, 4.78)	0.25	0.91 (0.36, 2.33)	0.85
Defaulted	150	33.6	188	45.2	0.74 (0.56, 0.98)	0.03	0.74 (0.57, 0.97)	0.03
Non-recovered §	111	24.8	114	27.4	0.90 (0.70, 1.15)	0.40	0.91 (0.73, 1.15)	0.45
Transfer-inpatient	18	4.0	11	2.6	1.40 (0.34, 5.69)	0.47	1.58 (0.38, 6.56)	0.53
Transfer-new facility	21	4.7	12	2.9	1.43 (0.64, 3.17)	0.38	1.51 (0.68, 3.35)	0.31
Early discharge	51	11.4	27	6.5	1.80 (0.95, 3.40)	0.07	1.95 (1.10, 3.43)	0.02
	Median	**IQR**	**Median**	**IQR**	**Common Language Effect Size statistic (control > intervention) * (95% CI)**			
Length of stay (days) [a]	81	66, 101	94	71, 108	0.56 (0.46, 0.67)			

MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score. *N* = number of clusters; *n* = individual children eligible for treatment. †Both unadjusted and adjusted results account for the effect of clustering. The adjusted model also includes adjustment for country, age and sex. ‡ Analyses use the Generalized Linear Model, reporting Pearson chi-squared *p*-values. § Non-recovered defined as not reaching recovery criteria after 17 weeks in treatment. [a] Length of stay among recovered children only, per global CMAM reporting standards [46]. * Probability that a randomly selected control length of stay is greater than a randomly selected intervention length of stay.



Supplementary Figure S1. Panel of WAZ and MUAC response among all children by admission group. MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score. (**a**) WAZ plotted against week in program for Group 1; (**b**) MUAC plotted against week in program for Group 1; (**c**) WAZ plotted against week in program for Group 2; (**d**) MUAC plotted against week in program for Group 2; (**e**) WAZ plotted against week in program for Group 3; (**f**) MUAC plotted against week in program for Group 3. The shaded areas represent a 95% confidence band around each curve (i.e., the area between the upper and lower 95% confidence limits is shaded). Overlaps between confidence intervals are more darkly shaded.

H: Cost-effectiveness analysis methods publication

Lelijveld N, Musyoki E, Adongo SW, Mayberry A, Wells JC, Opondo C, Kerac M, **Bailey J**. Relapse and post-discharge body composition of children treated for acutemalnutrition using a simplified, combined protocol: A nested cohort from theComPAS RCT. PLOS One. 2021; 16(2):e0245477.https://doi.org/10.1371/journal.pone.0245477.

Lelijveld *et al. Trials* (2018) 19:252
https://doi.org/10.1186/s13063-018-2594-7

Trials

STUDY PROTOCOL Open Access

The "ComPAS Trial" combined treatment model for acute malnutrition: study protocol for the economic evaluation

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Abstract

Background: Acute malnutrition is currently divided into severe (SAM) and moderate (MAM) based on level of wasting. SAM and MAM currently have separate treatment protocols and products, managed by separate international agencies. For SAM, the dose of treatment is allocated by the child's weight. A combined and simplified protocol for SAM and MAM, with a standardised dose of ready-to-use therapeutic food (RUTF), is being trialled for non-inferior recovery rates and may be more cost-effective than the current standard protocols for treating SAM and MAM.

Method: This is the protocol for the economic evaluation of the ComPAS trial, a cluster-randomised controlled, non-inferiority trial that compares a novel combined protocol for treating uncomplicated acute malnutrition compared to the current standard protocol in South Sudan and Kenya. We will calculate the total economic costs of both protocols from a societal perspective, using accounting data, interviews and survey questionnaires. The incremental cost of implementing the combined protocol will be estimated, and all costs and outcomes will be presented as a cost-consequence analysis. Incremental cost-effectiveness ratio will be calculated for primary and secondary outcome, if statistically significant.

Discussion: We hypothesise that implementing the combined protocol will be cost-effective due to streamlined logistics at clinic level, reduced length of treatment, especially for MAM, and reduced dosages of RUTF. The findings of this economic evaluation will be important for policymakers, especially given the hypothesised non-inferiority of the main health outcomes. The publication of this protocol aims to improve rigour of conduct and transparency of data collection and analysis. It is also intended to promote inclusion of economic evaluation in other nutrition intervention studies, especially for MAM, and improve comparability with other studies.

Trial Registration: ISRCTN 30393230, date: 16/03/2017.

Keywords: Cost-effectiveness, Severe acute malnutrition, Moderate acute malnutrition, Community management of acute malnutrition, Cost-consequence analysis

Background

Tackling undernutrition in all its forms is a major global health priority demonstrated by its inclusion in the recent Sustainable Development Goals [1]. Stunting, severe acute malnutrition (SAM) and intrauterine growth restriction together are responsible for 21% of disability-adjusted life-years for children under 5 years [2]. Annually, acute malnutrition specifically affects 52 million children aged under 5 years and is associated with a high mortality rate if untreated as well as multiple long-term implications [3, 4]. Acute malnutrition is currently defined as low weight-for-height, low mid upper arm circumference (MUAC), and/or presence of bilateral oedema. It can be either moderate (MAM) or severe (SAM), depending on the extent of wasting. SAM cases, without medical complications, are treated through outpatient therapeutic programmes, where they receive routine medical care and a weekly take-home

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ration of ready-to-use therapeutic food (RUTF). Although there is currently no consensus on how best to manage MAM cases, they are often treated in food-insecure settings through supplementary feeding programmes (SFP), where they receive bi-weekly take-home rations of ready-to-use supplementary food [5, 6]. When discussing SAM and MAM in combination, the term 'global acute malnutrition' (GAM) is applied.

The current system of two parallel malnutrition treatment programmes and product supply chains means that SAM programmes are often prioritised over those for MAM, resulting in no services for MAM children in many settings. In contexts where the treatment of both SAM and MAM are available, the parallel systems may be resulting in an inefficient use of resources. In addition, current dosage of RUTF for treatment of SAM is based on the weight of the child, requiring multiple calculations by health workers and, in some cases, children are provided with a higher dose and for a longer period of time than required [7].

ComPAS (Combined Protocol for Acute Malnutrition Study) aims to assess whether unifying and simplifying the treatment of uncomplicated SAM and MAM for children aged 6–59 months into one programme would have an impact on the effectiveness of treatment. The 'combined protocol' will treat all SAM and MAM cases with RUTF using a simple MUAC-based dosage protocol, and this will be compared to the 'standard protocol' in a non-inferiority, cluster-randomised controlled trial. Further details of the ComPAS trial study design are published elsewhere [7, 8].

Few studies have assessed the cost-effectiveness of nutrition interventions, particularly with regard to treatment of MAM and changes in acute malnutrition protocols. Since the introduction of the current standard community-based protocol for treatment of SAM in 2001, studies have found this model to be cost-effective compared to the previous model of inpatient treatment [9–11]. Treatment for SAM is estimated to cost between USD$26 and USD$53 per disability-adjusted life year averted [9–11], and between USD$100 and USD$203 per child treated [11, 12]. It has also been estimated that costs can be as high as USD$500 per child treated by non-government organisations in fragile or emergency contexts [13]. The cost per MAM child treated is not widely published, perhaps due to the current lack of recommended protocols.

One previous study has trialled a combined protocol, using RUTF to treat MAM and SAM, and found it to have a comparable recovery rate (83% vs. 79%) for GAM and higher coverage (71% vs. 55%, $P = 0.0005$) than the standard protocol [14]. This clinical trial was conducted in Sierra Leone in 2013 and tested the efficacy of an integrated, MUAC-only protocol for the treatment of SAM and MAM using one product (RUTF) at different standardised doses for children with a height < 115 mm (175 kcal/kg/day) and 115–125 mm (75 kcal/kg/day), against the standard protocol, which used corn-soy blended flour (CSB++) for children with MAM. The study also presents the cost of therapeutic food from a programme perspective. The cost of RUTF was US$4/kg, which was the local producer's price in 2013, and US$1.30/kg for CSB++ [14]. The cost of RUTF used to treat a SAM case was US$36 in the combined protocol, compared to US$68 in the standard programme. The cost of food products to treat a case of MAM was US$12 in both the combined and standard management arms.

Despite the higher price of RUTF compared to CSB++, the study found that the integrated protocol was less costly due to the lower dose of RUTF provided to SAM cases and faster recovery rates of children with MAM. The authors theorised that, due to the reduced food costs and simpler logistical requirements, it seemed likely that the integrated management would be less costly to implement per child treated than the standard protocol [14]. They also found a lower proportion of SAM in their combined protocol arm, which they hypothesised might be due to SAM cases averted by earlier treatment of MAM with RUTF. The need for a more complete economic analysis of the combined protocol was highlighted.

Our study builds on this previous work, and aims to estimate the full economic cost of the ComPAS combined protocol, compared to the standard protocol, from a societal perspective. We hypothesise that the combined protocol will be more cost-effective than the standard protocol as overall costs will be lower and an equivalent recovery rate from GAM will be achieved. Many cost-effective health interventions have better health outcomes but at a greater cost; we hypothesise that the combined protocol will have as high recovery rates as the standard protocol, at a lower cost (Fig. 1). Based on the literature, we hypothesise that cost reductions will come from the streamlining of logistics and personnel, the potential for provision of lower weekly dosages of RUTF, and the faster recovery of children.

As few protocols have been published for economic evaluations in child health, this article follows a call for publication of complex economic protocols [15]. The publication of economic protocols, such as this, aims to improve the rigour of conduct among costing studies, improve comparability, and familiarise researchers and programme implementers in global health nutrition with the methodologies of economic evaluation in order to encourage its inclusion in more nutrition intervention trials.

Aims and objectives

The aim of the ComPAS economic evaluation is to measure the cost and cost-effectiveness of a 'combined

Fig. 1 Depiction of hypothesised economic outcome of the 'combined protocol' on the cost-effectiveness matrix. We hypothesise that the 'combined protocol' for treatment of severe and moderate acute malnutrition will have as high recovery rates as the standard treatment protocol, but at a lower cost

protocol' for treatment of SAM and MAM compared to the standard protocol, which separates SAM and MAM treatment into an outpatient therapeutic programme and SFP. The primary marker of effectiveness will be recovery from GAM, defined as achieving a MUAC ≥ 125 mm. The secondary markers of effectiveness will be programme coverage, length of treatment, treatment adherence, average weekly weight gain and average weekly MUAC gain.

The specific objectives of the economic evaluation are to:

1. Quantify the economic cost of implementing the combined protocol (intervention) and the standard protocol (control), using a combination of activity-based costing and ingredients approach.
2. Quantify the economic cost to households partaking in the combined protocol and the standard protocol.
3. Estimate any incremental costs to the wider health system by the implementation of the combined protocol compared to the standard protocol using programme referral data and published literature.
4. Compute the incremental cost per child recovered for the combined protocol compared to the standard protocol.
5. Present the costs and any significant differences in the primary and secondary outcomes (i.e. recovery rate, coverage, defaulting, average weight gain, average MUAC gain and length of treatment) as a cost-consequence analysis.

Methods

Study design

This study is a cost-consequence and cost-effectiveness analysis of the ComPAS trial, a multi-country, cluster-randomised, controlled trial taking place between May 2017 and July 2018. We will estimate the total costs of both protocols from a societal perspective, including both service provider and household costs. Data collection for the costing study will take place at the mid-point of recruitment for the main trial, and accounting data will be accessed at the end of the study implementation. Time horizons for the costing study are within the trial period only.

Ethical approval for the trial was obtained from the Kenya Medical Research Institute (KEMRI) (5/1/2017, ref.: 551), the South Sudan Ministry of Health Internal Review Board (21/11/2016), and the London School of Hygiene and Tropical Medicine (28/11/2016, ref: 11826). This protocol describes the methods specific to the economic study alongside the ComPAS randomised controlled trial, following the SPIRIT checklist format (see Additional file 1); further details of the protocol have been published elsewhere [8].

Target population

The target population for the ComPAS trial is children aged 6–59 months who are diagnosed with uncomplicated acute malnutrition and are eligible for outpatient treatment. Acute malnutrition is defined in the trial as a MUAC < 125 mm and/or bilateral pitting oedema only. Children with a weight-for-height < −2 z-score will be treated, however, they will not be included in the primary analysis. The only reason for non-inclusion will be if the child is receiving SAM or MAM treatment at another facility.

All caregivers of children presenting with acute malnutrition at participating health facilities, who meet the inclusion criteria, are approached for consent to take part in the trial. Details of the informed consent process can be found in the trial protocol [8]. If the caretaker chooses not to participate in the trial, their child is enrolled for treatment only and their information is not recorded for study purposes.

For the economic evaluation, the target populations for the collection of resource-use data are (1) carers of children receiving treatment for acute malnutrition as part of the trial; (2) staff working to treat children enrolled in the trial; (3) support, supervision, management and logistics staff relevant to the treatment of children in the trial; and (4) partner organisations supporting any aspect of care provision to children enrolled in the trial.

Setting and randomisation

The study will take place in 12 health facilities in Nairobi County in Kenya and 12 health facilities in

Aweil East County, South Sudan. Six health facilities in each country have been randomised to the control arm and six to the intervention arm using a random sequence generated and applied to a pre-written list of participating clinics. Health facility staff are not blinded to the trial, as they are required to follow the specific protocol to which their facility is allocated.

Nairobi County is an urban area where more than 60% of residents live in informal settlements, in which the estimated prevalence of wasting (GAM) is 2.8% [16]. The 2014 Kenya Demographic and Health Survey estimated that 17% of children aged under 5 years in Nairobi were stunted, and 4% were underweight; further 60.4% of children were fully immunised and 93.6% of women living in urban areas were literate [17]. The 12 health facilities in Nairobi are operated by the Ministry of Health with support from International Rescue Committee specifically for treatment of malnutrition. These facilities were selected as study sites by the Ministry of Health based on the high burden of malnutrition; they are approximately 3–5 km apart.

Aweil East is a rural setting in Northern Bahr el Ghazal State in South Sudan. Children under 5 years of age are thought to account for 19% of the population and 76% of the population in the State live below the poverty line [18]. A Standardized Monitoring and Assessment of Relief and Transitions survey conducted in Aweil East in April 2014 reported a GAM prevalence of 26% [19]. Coverage of measles immunisations is thought to be 27%, and the 2009 National Baseline Household Survey found national female literacy rates to be 16% [20]. The 12 health facilities included in this study are operated by an internationalnon-government organisation (Action Against Hunger), are approximately 20–30 km apart from each other and provide malnutrition services only.

Intervention

The control arm follows the standard protocol defined by national guidelines for the treatment of SAM and MAM, and the intervention arm follows a combined protocol for SAM and MAM. The RUTF dosage for the intervention was developed based on a retrospective analysis of acute malnutrition treatment data in order to propose a physiologically appropriate, simplified dosage that meets the energy requirements for acutely malnourished children defined by MUAC [7]. Children treated in the control arm receive 200 kcal/kg/day of RUTF if they are classified as SAM (MUAC < 115 mm or bilateral pitting oedema), and 500 kcal/day of ready-to-use supplementary food if they are classified as MAM (MUAC 115 to < 125 mm), as per national protocols. Children treated in the intervention arm receive 1000 kcal/day of RUTF if they have SAM and 500 kcal/day of RUTF in they have MAM. Further details of the two protocols can be found in Table two of Bailey et al. [8] and in the online trial registration (ISRCTN 30393230) [21].

Health outcomes

The primary outcome of the ComPAS trial is 'proportion of children recovered'; however, as a non-inferiority trial, it is expected that this outcome will not be statistically significantly different between intervention and control arms. For the purposes of analysis, recovery will be defined as two consecutive measurements with a MUAC ≥ 125 mm and no oedema for both control and intervention arms.

The secondary outcomes will be treatment coverage, defaulter rate, length of treatment, average weight gain and average MUAC gain. Coverage is defined as proportion of children eligible for treatment (MUAC < 125 mm) who receive treatment, assessed by a standardised Semi-Quantitative Evaluation of Access and Coverage survey [22]. Defaulting is defined as absence from treatment appointments for 3 consecutive weeks. Further details of health outcomes can be found in the trial protocol [8]. Statistically significant secondary outcomes will be presented in the cost-consequence analysis and unit costs presented where appropriate, e.g. cost per unit coverage, although the conservative *a priori* hypothesis for all outcomes is non-inferiority.

Maust et al. [14] found a reduced caseload of SAM in their version of the combined protocol and hypothesised that this could be due to more intensive treatment of MAM resulting in prevention of SAM. We will also explore any adjusted differences in SAM caseloads between the intervention and control arm and, if a significant difference is found, the cost per SAM case averted will be estimated. They also found that SAM children who received the intervention recovered more rapidly and therefore had a reduced cost of RUTF [14]. We will also present the cost of RUTF per SAM case simply using the number of sachets prescribed and the local unit cost per sachet, in order to compare with previously published values. Nevertheless, it is important to note that the study by Maust et al. [14] compared their combined protocol to routine control clinics, whereas this study will compare a combined protocol to fully supported, 'optimal' control sites. Exploration of differences in defaulting rates and relapse rates between the two protocols will also be considered in relation to their effect on total programme costs.

Recent health seeking and referrals to external medical care will also be assessed in a sub-set of study participants in order to estimate differences in health seeking behaviour and utilisation of wider health services, which will inform the estimated cost of the intervention to the wider health system.

Sample size

There will be 12 health facilities (clusters) in South Sudan and 12 in Kenya; in each country, six health facilities will be randomly allocated as intervention and six as control, with 150 children per clinic. The sample size for the main trial outcome was calculated using an expected recovery rate of 85% based on the average programme statistics for each site, allowing for a 10% non-inferiority margin, with 80% power at the 5% level of significance.

As the study is only statistically powered for determining effectiveness across both countries rather than within each country, the economic evaluation will be conducted using pooled costs and outcomes from both sites. Pooled and site-specific costs and outcomes will also be presented in the cost-consequence analysis.

Cost data collection will be carried out at all 24 health facilities participating in the study. For beneficiary costs, an exhaustive sample will be asked a simple survey about cost and time implications of participating in the programme as part of the main trial exit interview. In addition, more in-depth group interviews with beneficiary carers will take place with between four and six purposively selected participants at each clinic (i.e. ~72 participants for each country) (Table 1). Interview sample sizes will be determined by data saturation. Survey sample sizes will be dictated by the trial sample size; however, post-hoc sample size calculations for differences in cost and time data will be calculated where possible.

Measuring resources and costs

The economic evaluation will be conducted from a societal perspective, measuring programme and household costs. A combination of activity-based costing and ingredients approach will be used to estimate programme costs. See Table 1 for list of activities and ingredients. The timing of data collection points can be seen in Fig. 2. Full start-up costs will not be collected as protocol development has been on-going across previous years and previous studies; however, simple start-up costs relevant for future use, such as stakeholder meetings, trainings, community sensitisation and translation of resources, will be estimated. Note that cost of inpatient treatment for SAM will not be collected as it is not part of the intervention.

Measuring programme costs

Major activities guiding the programme costs have been derived from other community management of acute malnutrition costing analyses [9, 23], namely treatment, outreach, supply logistics, training, supervision and management. The ingredients within each activity will be quantified and costed using a clinic audit, key informant interviews with clinic staff, Ministry of Health regional level staff and relevant partner organisations, and accounting data, where available (Table 1). Capital costs will be annualised over their expected useful life (3 years for computers, 5 years for cars and other equipment, 10 years for communal land) and discounted at a rate of 3%. The allocation of joint costs will be divided by activity and by study arm, informed by the weekly clinic survey and study-midpoint staff time-use interview.

As programme costs are the primary area where we anticipate the main differences to lie between intervention and control, we will collect primary resource use data for all activity areas rather than rely on assumptions applied to accounting data. Specifically, we hypothesise differences in therapeutic food and staff costs.

Measuring household costs

Basic travel time and costs will be measured using survey questions to all study participants during the main trial exit interview. In Kenya, survey data will be collected electronically and stored on a secure server. In South Sudan, survey data will be collected on paper and entered using the same electronic data collection system as in Kenya, which includes appropriate skip logic, value restrictions and data checks. Group interviews with a sub-sample of participants during their enrolment in the study will also be undertaken to consider any hidden or abstract costs to households as well as to calculate potential lost earnings due to time spent at the programme. Participants will be purposively selected to represent both SAM and MAM children as well as a range of travel times.

Estimating costs to the wider health system

Wider health system costs will be estimated using the number and nature of referrals of participating children as well as any differences in health-seeking behaviour. Referral nature and number will be estimated based on quarterly clinic surveys and health-seeking behaviour will be discussed in participant group interviews. Cost will be estimated using existing published data on costs of treating common referrals, for instance WHO CHOICE cost estimates [24].

Analytical methods

Incremental cost-effectiveness ratios will be calculated for the primary outcome (i.e. incremental cost per additional child recovered) and for secondary outcomes where a statistically significant difference is found. Potential secondary outcomes for inclusion are treatment coverage, defaulter rate, length of treatment, average weight gain and average MUAC gain. Univariate and multivariate sensitivity analyses will be performed in order to assess the potential best case and worse case variability in costs and outcomes. Areas of potential

Table 1 Outline of data categories and sources

Activity	Ingredients	Data sources	Sample size
Programme costs			
Treatment[a]	Therapeutic food Human resources Other medical supplies Other supplies Space	1. MoH/partner accounting data 2. Clinic audit 3. KII with partners (UN agencies) 4. Time allocation questionnaire	1. N/A 2. All clinics (12 per country) 3. One from each partner 4. Purposive sample representing all types of clinic staff involved in treatment
Outreach	Transport Supplies Human resources	1. MoH/partner accounting data 2. Clinic audit	1. N/A 2. All clinics (12 per country)
Supply logistics	Storage Transport Human resources	1. MoH/partner accounting data 2. KII with partners and clinic staff 3. Time allocation questionnaire	1. N/A 2. Purposive sample representing all partners 3. Purposive sample representing all types of clinic staff
Training	Space Supplies Human resources	1. MoH/partner accounting data 2. Clinic audit	1. N/A 2. All clinics (12 per country)
Supervision	Transport Human resources	1. KII with supervisors	1. Purposive sample representing all supervisors
Management	Human resources Equipment Space	1. MoH/partner accounting data 2. KII with MoH/partner support staff 3. Time allocation questionnaire	1. N/A 2. Purposive sample 3. All support staff involved in the programme
Household costs			
Participating in treatment	Supplies Time Transport	1. GIs with beneficiaries 2. Beneficiary exit survey	1. 4–6 randomly selected beneficiaries from each clinic 2. All beneficiaries
Wider health system costs			
Referral to other healthcare providers	Space Human resources Supplies	1. Clinic audit 2. Literature estimates	1. All clinics (12 per country) 2. N/A

[a]Note that this does not include SAM inpatient treatment
KII key informant interview, *MoH* Ministry of Health, *GIs* group interviews, *N/A* not applicable

variability will be determined through exploration of the effectiveness data and the researcher's evaluation of cost data uncertainty following data collection. For example, there could be variability in costs or time-use information provided by staff and other key informants due to recall error.

In addition to incremental cost-effectiveness ratios, the economic evaluation will be presented as a cost-consequence analysis where all costs and outcomes will be listed, including the multiple secondary trial outcomes, allowing policymakers to compare costs with health gains for the combined protocol.

Costs will be presented in 2017 prices in local currency (Kenyan shillings and South Sudanese Pounds) as well as 2017 US dollars, which will allow for comparison across the two country sites as well as comparison with other studies. Costs and outcomes will not be discounted as the intervention does not span more than 1 year.

Results are expected to be generalisable to multiple African contexts, particularly within the range of the

	Baseline	Admission visit	Follow-up visits	Discharge visit	4-month post-discharge visit
Health facility informed consent	x				
Randomization of clusters	x				
Eligibility screen		x			
Individual Informed consent		x			
Demographic data		x			
Nutritional and medical assessment		x	x	x	x
Cost questionnaire				x	
ASSESSMENTS		**Start of study**	**Mid-Study**	**End of study**	
Costing interviews			x		
Mid-term safety review			x		
SQUEAC coverage assessments			x		
Costing accounting data				x	
Adverse event monitoring		x	x	x	x

Fig. 2 Schedule of enrolment, interventions and assessments

sensitivity analyses. Household food security estimates for each site will aid identification of where results may be generalisable to (i.e. food insecure settings). In addition, as treatment in one study site is government-led and in the other it is partner-led, results from each should be of interest to implementers with a variety of programme structures. One limitation of the study is that the main analysis will present an average of the two sites, therefore masking some of the heterogeneity between sites.

Anonymised hardcopies of data will be stored in approved, secured locations in the respective countries; anonymised electronic data for the economic evaluation will be stored on a secure server in the UK, assessable only by the research team. No participant identifiable data will be recorded. Results will be reported following the consolidated health economic evaluation reporting standards (CHEERS) checklist [25].

Discussion

This economic evaluation will provide key information for policymakers when considering alterations to the GAM treatment protocols. As a non-inferiority trial, the recovery rates are expected to be statistically similar between each protocol, hence the comparative cost-effectiveness will likely play a larger role in policy decision-making.

With regard to limitations, this study will not be able to assess the cost impact of the combined protocol on international logistics and supply chain, which may be further streamlined if the combined protocol were to be scaled-up. In addition, the full extent of the hypothesised cost savings of the combined protocol is unlikely to be realised during the period of this study (8–10 months). A longer time horizon is necessary to reveal the impact of an improved treatment protocol on the reduction in acute malnutrition caseload through prevention of deterioration from MAM to SAM. Finally, as is the case with many controlled trials, the extra support offered to both the combined and standard protocols will likely result in higher costs, which should be noted when generalising the results to routine programmes.

This publication aims to improve rigour in conduct and transparency of data collection and analysis. The publication of this protocol also intends to promote

inclusion of economic evaluation in other nutrition intervention studies, particularly for MAM, and improve comparability with other studies. Regardless of whether the new protocol is more cost-effective than the standard protocol or not, the evidence provided by this evaluation will contribute significantly to the currently limited evidence regarding cost-effectiveness of nutrition-specific interventions.

Trial status

This is protocol version number 1, finalised on 01/06/2017. Recruitment of trial participants began on 15/05/2017 and is expected to be completed on 01/06/2018, at which point accounting data and survey data will be analysed. Interviews for the economic evaluation began on 20/06/2017 and will be completed on 20/12/2018.

Additional files

Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents. (DOC 132 kb)

Additional file 2: Caretaker consent form for group interviews (Kenya). (DOCX 26 kb)

Abbreviations

ComPAS: Combined Protocol for Acute Malnutrition Study; CSB++: corn-soy blend (fortified); GAM: global acute malnutrition; MAM: moderate acute malnutrition; MUAC: mid upper arm circumference; RUTF: ready to use therapeutic food; SAM: severe acute malnutrition; SFP: supplementary feeding programme

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Availability of data and materials

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' contributions

NL, JB, LT and CP conceived and designed the study; NL and JB are managing the data collection; AM, DND, HHB and CP advised on specific aspects of the study protocol; and NL wrote the first draft of the manuscript. All authors contributed to the writing of the final version of the manuscript, and have read and approved it before submission.

Ethics approval and consent to participate

The ComPAS study, including the economic evaluation, was approved by the Kenya Medical Research Institute (KEMRI) (5/1/2017, ref: 551), the Ministry of Health Internal Review Board, South Sudan (21/11/2016), and the London School of Hygiene and Tropical Medicine (28/11/2016, ref: 11826). This protocol, specific to the economic analysis, was reviewed by the International Rescue Committee Institutional Review Board (Ref H1.00.017). Informed written consent is obtained prior to all surveys and interviews (see model consent form in Additional file 2).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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I: Follow-up study publication

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RESEARCH ARTICLE

Relapse and post-discharge body composition of children treated for acute malnutrition using a simplified, combined protocol: A nested cohort from the ComPAS RCT

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Abstract

Introduction

Severe and moderate acute malnutrition (SAM and MAM) affect more than 50 million children worldwide yet 80% of these children do not access care. The Combined Protocol for Acute Malnutrition Study (ComPAS) trial assessed the effectiveness of a simplified, combined SAM/MAM protocol for children aged 6–59 months and found non-inferior recovery compared to standard care. To further inform policy, this study assessed post-discharge outcomes of children treated with this novel protocol in Kenya.

Methods

Six 'combined' protocol clinics treated SAM and MAM children using an optimised mid-upper arm circumference (MUAC)-based dose of ready-to-use therapeutic food (RUTF). Six 'standard care' clinics treated SAM with weight-based RUTF rations; MAM with ready-to-use supplementary food (RUSF). Four months post-discharge, we assessed anthropometry, recent history of illness, and body composition by bioelectrical impedance analysis. Data was analysed using multivariable linear regression, adjusted for age, sex and allowing for clustering by clinic.

Results

We sampled 850 children (median age 18 months, IQR 15–23); 44% of the original trial sample in Kenya. Children treated with the combined protocol had similar anthropometry, fat-free mass, fat mass, skinfold thickness z-scores, and frequency of common illnesses 4 months post-discharge compared the standard protocol. Mean subscapular skinfold z-

version will be provided to interested parties, subject to the completion of a request form (available via the repository link above) and signing of a Data Transfer Agreement. Further inquires can be made to the Airbel research department at the International Rescue Committee (airbel@rescue.org).

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scores were close to the global norm (standard care: 0.24; combined 0.27). There was no significant difference in odds of relapse between protocols (SAM, 3% vs 3%, OR = 1.0 p = 0.75; MAM, 10% vs 12%, OR = 0.90 p = 0.34).

Conclusions

Despite the lower dosage of RUTF for most SAM children in the combined protocol, their anthropometry and relapse rates at 4 months post-discharge were similar to standard care. MAM children treated with RUTF had similar body composition to those treated with RUSF and neither group exhibited excess adiposity. These results add further evidence that a combined protocol is as effective as standard care with no evidence of adverse effects post-discharge. A simplified, combined approach could treat more children, stretch existing resources further, and contribute to achieving Sustainable Development Goal Two.

Introduction

Severe and moderate acute malnutrition (SAM and MAM) affect more than 50 million children worldwide and result in increased risk of illness, reduced physical and mental development, and death [1, 2]. While treatment for SAM has made huge strides in the past decade, with the introduction of ready-to-use therapeutic food (RUTF) and community management (CMAM), there is currently no consensus on how best to manage children with MAM. The lack of evidence in this area has prevented development of international guidelines, hence urgent research is needed. In addition, treatment coverage for both SAM and MAM remains low, with at least 80% of children 6–59 months old with acute malnutrition not accessing care [3]. In many settings, children with MAM receive no support, or they receive ready-to-use supplementary food (RUSF), which is dependent on a dedicated team to deliver this service and an independent supply chain [4, 5]. One option to improve the reach of treatment services, as well as potentially improve outcomes for MAM children, is combining the treatment of SAM and MAM into one protocol, using one ready-to-use food product.

The ComPAS trial (Combined Protocol for Acute Malnutrition Study) was a single-blinded, cluster randomised, controlled, non-inferiority trial to compare recovery rates of a combined protocol for uncomplicated SAM and MAM in children 6–59 months in South Sudan and Kenya against the standard treatment protocols in each country [6, 7]. It used a simplified dosage scheme based on mid-upper arm circumference (MUAC) and provided ready-to-use food (RUTF) for both SAM and MAM patients. The simplified dosage provided 2 sachets of RUTF per day for SAM children and 1 sachet per day for MAM children; this was often a lower dosage than what was provided by the standard weight-based dosage calculations for SAM. The combined protocol had non-inferior recovery rates compared to standard treatment (76.3% vs 73.5%), as well as a reduced overall economic cost [8].

To better inform future policy, there is also a need to understand post-discharge outcomes for children treated with a simplified, combined protocol. Outstanding questions include: (1) Do children treated with the combined protocol have comparable sustained recovery and risk of post-discharge morbidity? (2) Are MAM children treated with RUTF rather than RUSF at increased risk of excess adiposity? It is possible that the provision of RUTF could promote the accretion of fat mass rather than lean mass, potentially leading to excess adiposity, which might track into adulthood. This is particularly important to rule out given the rise of non-communicable disease in low-income countries and concerns over the "double burden" of malnutrition [9, 10]. (3) Does the reduced dosage of RUTF for SAM patients in the combined

protocol affect the relapse rate after treatment? There have been few studies conducting post-discharge follow-up of acute malnutrition survivors [11], especially for MAM treatment. Hence our current understanding of predictors of post-discharge relapse, in general, is also limited [12].

This study aimed to answer the above questions by following-up children treated for SAM and MAM with either the standard protocol or a novel combined protocol, four months post-discharge in Nairobi, Kenya.

Methods

Trial design

This was a follow-up study for a subset of participants in the ComPAS trial; the methods and results of which have been described elsewhere [6, 8] (registered protocol at ISRCTN (ISRCTN30393230)). Briefly, the intervention arm of the trial treated all uncomplicated children whose MUAC was <12.5cm with RUTF: those with MUAC < 11.5cm and/or mild or moderate oedema (+/++) received 2 sachets of RUTF per day and those with MUAC between 11.5 and <12.5cm (and no oedema) received 1 sachet of RUTF per day. The control arm received the standard weight-based dose of RUTF for SAM and RUSF for MAM. Ethical approval for this follow-up study was granted as an amendment to the original study approval by the London School of Hygiene and Tropical Medicine (reference 11826) and the Kenya Medical Research Institute (reference non-KEMRI 551). Informed, written consent from a parent or guardian was required prior to participation in the study.

Setting

The original trial took place in 12 clinics in Kenya and 12 in South Sudan. This follow-up was only conducted for participants in the Kenya clusters. This was due to logistical constraints in South Sudan of following-up patients in a highly mobile population, as well as vast distances between communities and lack of mobile phone infrastructure. The Kenyan setting was urban health clinics in three sub-counties of Nairobi: Embakasi North, Embakasi East and Embakasi West.

Participants

Participants comprised surviving children who had been treated for uncomplicated SAM or MAM, defined as mid-upper arm circumference <12.5cm and/or presence of nutritional oedema (+/++), at any of the 12 participating health clinics, and who attended a follow-up appointment four months post-discharge. Children who presented after 6 months post-discharge were not included. To be eligible for treatment, children had to be between the ages of 6–59 months at admission, hence they could be between 10–63 months of age at the time of follow-up.

Study procedures

At discharge from treatment, caregivers were given an appointment date for their four month follow-up. If participants failed to attend this appointment, a community health worker telephoned the participant, if possible, or attempted to find the participant at home, and encouraged them to attend. Once at their appointment, anthropometry and body composition were measured and a questionnaire completed (see questionnaire in S1 File). Any children who were found to have relapsed into SAM or MAM were readmitted for standard treatment. Any

children who relapsed prior to their four-month appointment and sought care were recorded as a relapse case and still measured at four-months post the original discharge date.

Outcomes

Anthropometric assessments (weight, height, MUAC, oedema) were done following standard WHO procedures and were subject to quality control, which involved a trained study team member taking two readings within an allowable difference [13]. Weight for height (WHZ), weight for age (WAZ), and length for age (LAZ) z-scores were computed using the WHO 2006 growth standards [14]. Relapse was defined as SAM cases that relapsed back to SAM, or MAM cases that relapsed back to GAM ("global acute malnutrition", i.e. either MAM or SAM).

Bioelectrical Impedance Analysis (BIA) was used to estimate fat and fat-free mass using a BodyStat™ 1500 measuring at 50khz (Bodystat, Douglas, Isle of Man) [15]. Two consecutive readings were taken for each child; readings that were not within 10 ohms of each other were repeated after checking the child's position. Only repeatable BIA measures (<10 ohms difference in impedance) were included in analysis. Height-adjusted vectors (resistance index (R/H) and reactance index (Xc/H)) were computed using the approach of Piccoli et al., [16], while raw impedance (Z) was divided by the square of height to give the impedance index, from which fat-free mass (FFM) values (kg) were predicted using a calibration equation derived from healthy children aged 3 to 18 months in The Gambia [17]. A second equation, from malnourished children in Ethiopia aged 6 months to 14 years, was also used as a check, and yielded similar values [18]. Fat mass (FM) was calculated as the difference of FFM and weight. Phase angle was measured as a composite marker of cell mass and cellular health [19].

Subcutaneous fat levels and fat distribution were measured using skinfold thickness at the tricep and subscapular sites (Holtain Tanner/Whitehouse callipers, Holtain Ltd, Pembrokeshire, UK), representing peripheral and core body fat stores. Measurements were converted to z-scores for age and sex using the WHO 2006 growth standards [14]. Skinfold thickness ratios (subscapular/tricep) were calculated to represent peripheral vs central adiposity.

Food insecurity was assessed by the FAO Food Insecurity Experience Scale (FIES), an 8-question questionnaire which has been widely validated [20]. Other questions included those about any common morbidities suffered by the child in the past week and past 4 months, as reported by the caregiver (see questionnaire in S1 File).

Sample size

The ComPAS trial in Kenya enrolled 1,973 eligible children. Allowing for 30% loss to follow-up and excluding children discharged after February 2018 (due to logistical constraints), our potential sample size was approximately 840 children for this study. A previous study using BIA [21], reported mean resistance indices of 567 ohm/m (SD 130) and 603 ohm/m (SD 105) in SAM survivors and control children. We estimated that a sample of 840 children across 12 clusters would be sufficient to detect 36 ohm/m difference in Resistance index (R/H) based on mean values in that previous study, with 90% power at the 5% level of significance, and assumed intra-cluster correlation coefficient of 0.05, based on a previous trial [22].

Statistical analysis

We used hierarchical, multivariable regression analysis in Stata v14 software (StataCorp LP, College Station, Texas USA) to assess differences in continuous outcome data between combined protocol and control arms (anthropometry and body composition). Age and sex were adjusted for in the regression model, as well as accounting for clustering at clinic level. Differences in proportion of children with morbidities post-discharge were compared using logistic

regression, accounting for clustering. The odds of relapsing for the combined protocol children vs standard protocol children, and for children with various potential risk factors (including food security status, age, sex, MUAC at admission, MUAC at discharge, weight gain during treatment) was assessed using univariate and multivariable logistic regression. As well as comparing combined protocol to standard protocol, results were disaggregated by SAM and MAM status at treatment enrolment. This was due to differences in treatment protocol for SAM and MAM children; namely, MAM combined-protocol children were treated with RUTF, whereas MAM standard-protocol children received RUSF. Both arms treated SAM children with RUTF, but the dosage was lower on average for the combined protocol vs the standard protocol (105 vs 148 sachets to recovery (MUAC>12.5cm)); 81% in SAM cases received a reduced dosage compared to standard care [8].

Results

We recruited 850 children into the four-month follow-up study, which met our sample size requirements and was 43% of the original trial sample for ComPAS in Kenya (Fig 1). Children lost to follow-up were similar at baseline to those in our sample, except that this sample had fewer children with oedema and does not represent the small (2%) who died during treatment (S1 Table in S1 File). Children who were SAM based on weight-for-height z-score but not MUAC were excluded from the analysis. Due to several elections and political unrest during the implementation period of the ComPAS trial, many participants moved back to rural areas and were unable to attend their follow-up appointment [8]. Table 1 presents the demographic data for the follow-up sample disaggregated by study arm and SAM/MAM admission status.

At admission, in this sub-sample, children in the combined protocol clinics in Kenya were significantly more wasted (WHZ $p<0.0001$), underweight ($p<0.0001$) and stunted ($p = 0.042$) than children in the standard protocol clinics (Table 1). Mean MUAC at admission was similar between the two groups (p = 0.053). The cohort of children in the combined protocol had a greater proportion of females than the standard protocol, and had slightly greater proportion of oedematous SAM cases.

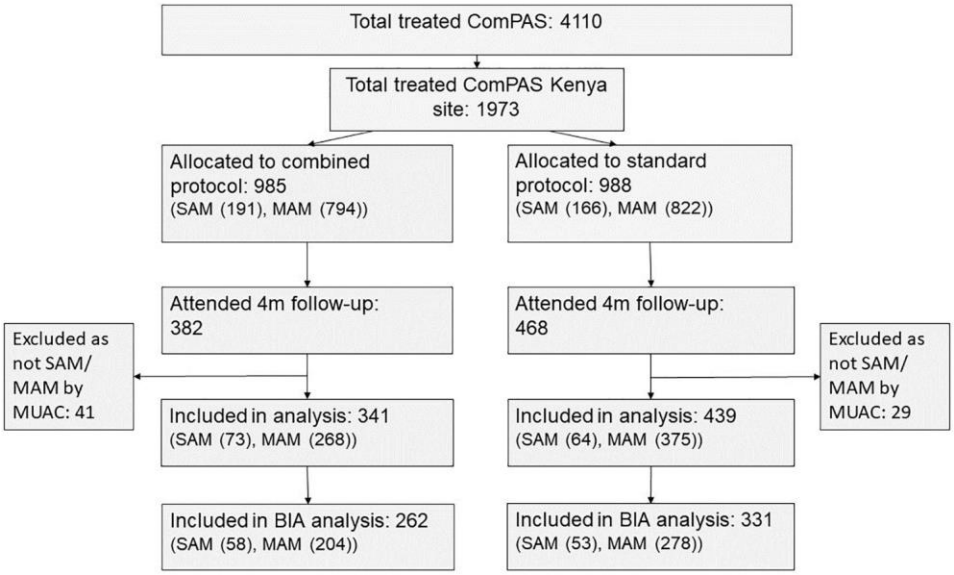

Fig 1. Recruitment flow diagram.

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Table 1. Demographic information for the follow-up sample.

	Combined protocol (N = 6, n = 382)			Standard protocol (N = 6, n = 468)		
	Total	SAM	MAM	Total	SAM	MAM
		n = 73	n = 268		n = 64	n = 375
Median age at follow up (months)	18 (IQR 15–23)	17.5	18	18 (IQR 15–23)	18	18
Males	38%	37%	37%	42%	36%	43%
HIV positive	1%	1%	1%	0%	0%	0%
Weight at admission (kg)	6.9 (1.4)	5.9 (0.9)	6.9 (1.2)	7.1 (1.2)	6.0 (0.7)	7.2 (1.3)
Height at admission (cm)	70.4 (7.6)	66.8 (4.7)	70.0 (6.7)	70.7 (6.7)	66.2 (4.6)	70.9 (6.1)
MUAC at admission (cm)	12.0 (0.6)	11.1 (0.5)	12.1 (0.2)	12.0 (0.5)	11.2 (0.4)	12.1 (0.2)
Oedema at admission	0.8%	-	-	0.2%	-	-
WHZ at admission	-2.32 (0.8)	-3.01 (0.8)	-2.12 (0.7)	-1.91 (0.9)	-2.42 (0.9)	-1.77 (0.8)
WAZ at admission	-2.69 (0.9)	-3.39 (0.9)	-2.53 (0.8)	-2.29 (0.9)	-3.11 (0.9)	-2.14 (0.8)
LAZ / HAZ at admission	-1.85 (1.2)	-2.16 (1.2)	-1.79 (1.3)	-1.65 (1.4)	-2.31 (1.3)	-1.53 (1.5)
MUAC at discharge (cm)	13.0 (0.5)	12.8 (0.7)	12.9 (0.4)	13.0 (0.5)	12.6 (0.7)	13.0 (0.5)
Weight gain (g/kg/day)	2.17 (1.3)	2.80 (1.2)	2.00 (1.2)	1.79 (1.3)	2.06 (1.4)	1.73 (1.3)

N = number of clusters; n = number of children. Data is presented as mean (SD) unless % is stated or age, which is median (IQR). WHZ = weight for height z-score; WAZ = weight-for-age z-score; LAZ = length for age z-score. MUAC = mid-upper arm circumference. LAZ used for <24 months, HAZ used for 24 months.

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Comparing anthropometry between the two protocols at four-month follow-up (Table 2), weight, height, MUAC, WHZ and WAZ were similar between the two groups at this point. This was true for the groups as a whole, and when disaggregated by SAM and MAM children at admission. There was also no statistical difference in LAZ at follow-up between the two protocols when comparing both groups as a whole, nor when comparing SAM admissions. However, there was a difference in LAZ when comparing the MAM children in the standard protocol to the MAM children in the combined protocol (Table 2). When comparing the mean change in LAZ for children between admission and 4-month follow-up, there was no significant difference between the protocols (change in LAZ since admission, MAM standard vs MAM combined, coefficient = -0.02, 95% CI -0.20 to 0.16, $p = 0.83$) (Fig 2).

When comparing morbidity outcomes at the four-month follow-up for the standard vs combined protocol (Table 3), we found no association between frequency of diarrhoea, vomiting, fever or cough in the past week and treatment protocol. This was true for both SAM and MAM admissions. There was also no association between the proportion of children admitted to hospital in the 4 months since discharge and treatment protocol.

As seen in Fig 1, 76% of children assessed at follow-up had repeatable BIA measurements that could be included in the analysis. There was no significant difference in body composition outcomes four months post-discharge between those treated with the combined and those treated with the standard protocol (Table 4 **& whole sample comparison in S2 Table in** S1 File). This includes FFM and fat mass levels (**S1 Fig** in S1 File), determined by BIA, as well as raw BIA outcomes (height-adjusted vectors, phase angle) (**S2 Fig in** S1 File) and skinfold thickness z-scores and ratio. Since this question was especially important for MAM cases, we present analysis for both groups as a whole and for MAM admissions only. Regarding adiposity levels at follow-up in general, 0.9% of the sample had triceps skinfold thickness above 2 z-scores, and 6.5% had a subscapular skinfold thickness above 2 z-score (see histograms in **S3 and S4 Figs in** S1 File). FFM comprised 73.5% of children's body weight for SAM survivors and 72.7% for MAM survivors.

Table 2. Anthropometry at four-month follow-up for combined vs standard protocol, disaggregated by SAM and MAM status.

	SAM cases				MAM cases			
	SAM cases				MAM cases			
	Standard protocol	Combined protocol	Adjusted Difference	P value	Standard protocol	Combined protocol	Adjusted Difference	P value
	mean (SD)	mean (SD)	(95% CI)[♦]		mean (SD)	mean (SD)	(95% CI)[♦]	
	n = 64	n = 73			n = 375	n = 268		
Weight (kg)	8.1 (1.2)	8.5 (1.1)	0.24 (-0.1, 0.6)	0.18	8.7 (1.1)	8.6 (1.3)	-0.15 (-0.4, 0.1)	0.29
Weight change since admission (kg)	2.1 (1.0)	2.6 (0.9)	0.44 (0.0, 0.9)	0.04	1.5 (0.7)	1.7 (0.8)	0.2 (0.0, 0.4)	0.02
Weight change since discharge (kg)	0.9 (0.6)	0.9 (0.7)	0.01 (-0.2, 0.3)	0.94	0.8 (0.6)	0.9 (0.6)	0.07 (-0.0, 0.2)	0.22
Height (cm)	74.4 (4.4)	75.4 (3.8)	0.49 (-0.7, 1.7)	0.43	77.2 (5.5)	76.6 (6.3)	-0.85 (-2.1, 0.4)	0.20
MUAC	13.0 (1.1)	13.2 (0.9)	0.14 (-0.3, 0.6)	0.53	13.4 (0.7)	13.3 (0.7)	-0.10 (-0.3, 0.1)	0.41
WHZ	-1.55 (1.3)	-1.25 (1.3)	0.18 (-0.3, 0.6)	0.44	-1.37 (0.9)	-1.40 (0.94)	-0.01 (-0.2, 0.2)	0.90
WAZ	-2.30 (1.2)	-2.00 (0.9)	0.13 (-0.2, 0.5)	0.50	-1.84 (0.9)	-2.01 (0.9)	-0.20 (-0.4, 0.03)	0.09
LAZ	-2.36 (1.2)	-2.17 (1.2)	0.04 (-0.4, 0.5)	0.84	-1.71 (1.2)	-1.99 (1.3)	-0.35 (-0.7, -0.02)	0.04

n = number of children.

[♦]adjusted for age and sex, allowing for clustering. Unadjusted weight is significantly smaller in standard arm due to younger age, difference is not present after adjusting.

WHZ = weight for height z-score; WAZ = weight-for-age z-score; LAZ = length for age z-score. MUAC = mid-upper arm circumference.

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Relapse

We examined the proportion of children that relapsed following treatment (Table 5). For those successfully discharged as cured, 3% of SAM cases and 11% of MAM cases relapsed within four months. There was no significant difference in odds of relapse for those in the combined protocol and those in the standard protocol (Table 5).

We assessed whether food security score might be a useful predictor of relapse, however, we found no association (Table 6). Being female, having a lower MUAC at admission, having a lower MUAC at discharge, and having a lower weight gain per day were all significantly associated with odds of relapsing in the whole sample. For those who were discharged as cured, being female and having a lower MUAC at discharge remained positively associated with odds of relapsing (Table 6).

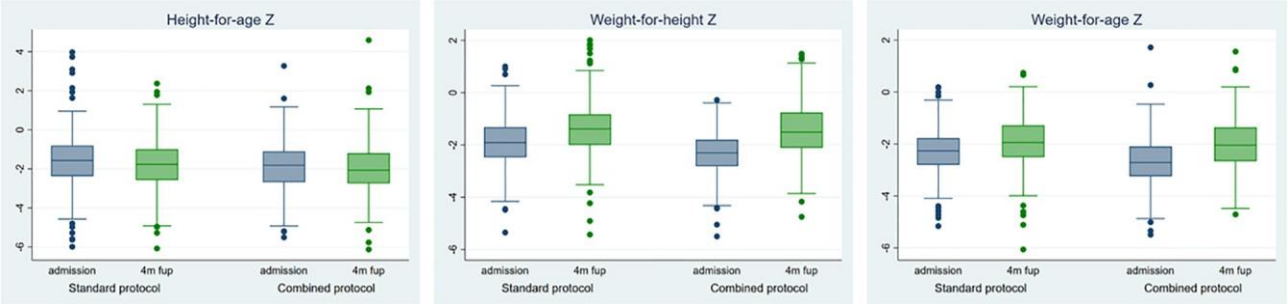

Fig 2. Anthropometry at admission and four-month follow for those in the standard and those in the combined treatment protocol.

https://doi.org/10.1371/journal.pone.0245477.g002

Table 3. Morbidity at four months post-discharge.

	SAM cases				MAM cases			
	Standard protocol	Combined protocol	Adjusted difference	P value	Standard protocol	Combined protocol	Adjusted difference	P value
	%	%	(95% CI)		%	%	(95% CI)	
	n = 64	n = 73			n = 375	n = 268		
Diarrhoea in past week	10.9%	5.6%	-0.71 (-2.4, 1.0)	0.41	8.0%	9.2%	0.05 (-0.9, 1.0)	0.91
Vomiting in past week	7.8%	8.5%	0.09 (-1.2, 1.3)	0.89	4.8%	7.6%	0.21 (-1.4, 1.8)	0.80
Fever in past week	9.4%	9.9%	0.24 (-1.1, 1.5)	0.72	10.2%	12.6%	0.34 (-0.9, 1.6)	0.59
Cough in past week	23.4%	16.9%	-0.29 (-1.8, 1.3)	0.72	18.2%	14.9%	-0.41 (-1.7, 0.9)	0.53
Hospitalised in past 4 months	4.7%	5.6%	0.19 (-1.3, 1.7)	0.81	2.4%	3.8%	0.52 (-1.8, 2.9)	0.66

Logistic regression analysis, accounting for clustering. n = number of children.

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Discussion

This follow-up study aimed to assess whether acutely malnourished children treated with a simplified, combined protocol have similar anthropometry, sustained recovery and morbidity risk as children treated with the standard protocol at four months post-discharge. We were particularly interested in outcomes of SAM children in the combined protocol who have, on average, a reduced dosage of RUTF compared to the standard protocol, and MAM children treated with RUTF in the combined protocol, rather than RUSF as per the standard protocol.

Despite the children in the combined protocol having more severe anthropometric deficits at admission, we found no significant difference in weight, height, MUAC, WHZ and WAZ at

Table 4. Body composition at four-month follow-up.

	SAM cases				MAM cases			
	Standard protocol mean (SD)	Combined protocol mean (SD)	Adjusted difference	P value	Standard protocol mean (SD)	Combined protocol mean (SD)	Adjusted difference	P value
	n = 53	n = 56	(95% CI)[◆]		n = 276	n = 198	(95% CI)[◆]	
Fat free mass (kg) §	6.03 (0.68)	6.12 (0.62)	0.07 (-0.22, 0.35)	0.63	6.33 (0.78)	6.25 (0.89)	-0.10 (-0.31, 0.11)	0.37
Fat mass (kg) §	2.2 (0.68)	2.35 (0.94)	0.13 (-0.15, 0.42)	0.37	2.37 (0.86)	2.33 (0.97)	-0.07 (-0.33, 0.20)	0.63
R/h	1247.3 (182.9)	1223.4 (151.0)	-19.5 (-88.6, 49.5)	0.58	1195.3 (155.5)	1210.9 (162.6)	13.73 (-29.8, 57.2)	0.54
Xc/h	72.65 (16.1)	73.29 (16.1)	0.10 (-8.71, 8.92)	0.84	72.87 (15.8)	75.32 (21.2)	2.27 (-2.10, 6.65)	0.31
Phase angle ˚	3.46 (0.78)	3.55 (0.79)	0.09 (-0.20, 0.39)	0.98	3.48 (0.63)	3.55 (0.78)	0.05 (-0.14, 0.24)	0.58
Skinfold thickness ratio	1.14 (0.21)	1.07 (0.19)	-0.06 (-0.15, 0.02)	0.13	1.14 (0.21)	1.15 (0.22)	0.005 (-0.08, 0.09)	0.91
Tricep skinfold z score	-0.47 (1.43)	-0.34 (1.19)	0.04 (-0.96, 1.03)	0.94	-0.25 (1.25)	-0.25 (1.10)	-0.004 (-0.72, 0.72)	0.99
Subscap skinfold z-score	0.07 (1.46)	0.49 (1.17)	0.33 (-0.53, 1.20)	0.45	0.30 (1.20)	0.21 (1.19)	-0.06 (-0.80, 0.68)	0.88

n = number of children.

[◆]adjusted for, age and sex; allowing for clustering. § fat-free and fat mass calculated using an equation from healthy children in The Gambia (17). Skinfold thickness ratio = tricep/subscapular. R/h = resistance index; Xc/h = reactance index.

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Table 5. Relapse at four months post-discharge and comparison between treatment arms.

All follow-ups				Discharged as cured			
From SAM to SAM		From MAM to GAM		From SAM to SAM		From MAM to GAM	
Combined	Standard	Combined	Standard	Combined	Standard	Combined	Standard
4/71	6/64	33/261	50/373	1/34	1/34	21/218	39/318
(6%)	(9%)	(13%)	(13%)	(3%)	(3%)	(10%)	(12%)
OR = 0.52 p = 0.31		OR = 0.08 p = 0.78		OR = 1.0 p = 0.75		OR = 0.90 p = 0.34	

OR = odds ratio. SAM = severe acute malnutrition; MAM = moderate acute malnutrition; GAM = global acute malnutrition, which is a combination of moderate and severe.

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four months post-discharge between the two protocols. We did find that LAZ was significantly lower for MAM survivors in the combined protocol than the standard protocol, however this reflects significant differences that existed at admission as "change in LAZ" since admission was similar between the groups. Weight gain was also higher in the combined vs standard protocol, which is again likely due to greater severity of weight deficits at admission, and either faster catch-up or possibly some regression to the mean. Morbidity since discharge was also similar; importantly, this was likewise true for SAM children in the combined protocol who on average received a lower dosage of RUTF than those in the standard protocol. These outcomes are in line with the conclusions of the main trial which found non-inferior recovery between the combined and standard protocols (76.3% vs 73.5%, risk difference of .03 (95% CI -0.05 to 0.10, p = 0.52)) [8].

Body composition outcomes were also similar at four months post-discharge and MAM children treated with RUTF did not have significantly different amounts or ratios of adiposity than those treated with RUSF. The mean subcutaneous fat levels remained close to the WHO global norm (mean tricep = -0.28 z-score; mean subscapular = 0.25 z-scores) suggesting no evidence of excessive fat gain at this stage post-treatment. Catch-up in in fat mass after SAM

Table 6. Predictors of relapse at four months post-discharge.

	All follow-ups				Discharged as cured			
	Relapsed (GAM to GAM) N = 666	Didn't Relapse N = 117	Odds ratio	P value	Relapsed (GAM to GAM) N = 534	Didn't Relapse N = 73	Odds ratio	P value
	Mean (SD) or %	Mean (SD) or %	(95% CI)		Mean (SD) or %	Mean (SD) or %	(95% CI)	
Food security score	3.14 (3.1)	3.16 (3.1)	0.99 (0.9, 1.1)	0.97	2.94 (3.1)	3.04 (3.0)	0.99 (0.9, 1.1)	0.84
Female Sex	70.0%	58.0%	1.69 (1.0, 2.7)	**0.03**◆	73.6%	57.3%	2.07 (1.1, 3.9)	**0.03**◆
MUAC at admission	11.80 (0.5)	11.96 (0.4)	0.53 (0.4, 0.8)	**0.001**◆	12.00 (0.3)	12.03 (0.4)	0.87 (0.5, 1.6)	0.66
MUAC at discharge	12.54 (0.6)	12.99 (0.5)	0.14 (0.1, 0.2)	**<0.001**◆	12.81 (0.4)	13.05 (0.4)	0.11 (0.04, 0.3)	**<0.001**◆
Age at admission	11.63 (9.0)	11.79 (6.4)	1.00 (0.8, 1.0)	0.81	12.37 (8.6)	12.21 (6.4)	1.00 (0.96, 1.0)	0.85
Weight gain (g /kg/ day)	1.58 (1.2)	2.02 (1.3)	0.74 (0.6, 0.9)	**0.001**◆	1.79 (1.3)	2.12 (1.3)	0.81 (0.7, 1.0)	0.05

MUAC = mid-upper arm circumference. Food security score was generated from the FAO Food Insecurity Experience Scale (FIES) questionnaire. GAM = global acute malnutrition, which includes both severe and moderate forms.

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recovery may be beneficial at mitigating high post-discharge mortality, and this may be at a cost of muscle mass gain, as seen in long-term SAM follow-up studies [21, 23, 24].

Relapse rates up until four months post-discharge were 3% for children admitted with SAM and 11% for children admitted with MAM, when restricting the analysis to those discharged as cured. If we include the whole sample (i.e. also those who defaulted treatment or who did not respond to treatment), relapse proportions were greater (8% for SAM and 13% for MAM), however it can be argued that this is not true relapse as children who defaulted or failed treatment may not have recovered to begin with. The reduced dosage in the combined protocol may have impacted relapse rates [25], however we found the odds of relapsing were similar between the two protocol arms. Another study with a reduced RUTF dosage regime also reported no impact on relapse rates compared to standard dosage in uncomplicated SAM cases in Burkina Faso (2.4% relapse vs 1.8%; $p = 0.69$) [26]. They did however find a small but significant negative effect on linear growth, which we did not find. Among those who recovered, being female and having a lower MUAC at discharge (mean MUAC 12.54 vs 12.99) were positively associated with odds of relapsing, suggesting that these children might benefit from more proactive follow-up at discharge. Comparing relapse rates with those in other studies is difficult due to varying follow-up periods and differing definitions for both the numerator and the denominator, as highlighted by a recent review [12]. Papers in that review with a follow-up period up to six months found SAM relapse rates between 1.9% and 17% [12, 27, 28]. Across the studies, the strongest, most consistent risk factor associated with relapse was having lower anthropometric measurements upon admission to and discharge from treatment, which is in line with one of our findings.

It is important to note that this was a semi-passive follow-up process, hence relapse rates may not be accurate. Participants were asked to attend their follow-up appointments at the clinic and were called or visited to encourage attendance if they missed their appointment. Loss to follow-up would likely have been lower if study measurements took place at participant's homes. Budget constraints, which prevented follow-up of the final children enrolled between February and May 2018, as well as the two general elections that took place in 2017, also contributed to loss to follow-up. This limitation affects both the study arms equally and those lost to follow-up had similar baseline characteristics as the sample retained, although a small element of survivor bias may be present. Since children in this study were recruited based on MUAC definitions of wasting, these findings may not be generalisable to children diagnosed with SAM based on WHZ. Another limitation of this study is the short follow-up period. In trying to move towards a more standard definition of relapse, follow-up until 6 months post-discharge is recommended [12, 25]. Additionally, longer-term follow-up is needed to further explore effects of treatment on body composition and health.

Conclusion

Acutely malnourished children treated with a simplified, combined protocol have similar sustained recovery and post-discharge morbidity risk as children treated with current standard care. SAM children treated with the combined protocol had similar anthropometry and relapse rates four months post-discharge to those treated with the standard protocol, despite reduced dosages of RUTF. MAM children treated with RUTF in the combined protocol had similar body composition to those treated with RUSF in the standard protocol and neither group exhibited excess adiposity at four months post-discharge. These results strengthen the conclusions of the main trial that a combined protocol is non-inferior in terms of recovery to standard care. Moving towards a simplified, combined approach could treat more children,

stretch existing resources further, and contribute to achieving Sustainable Development Goal Two of ending all forms of malnutrition.

Supporting information

S1 File.
(DOCX)

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