



LONDON
SCHOOL *of*
HYGIENE
& TROPICAL
MEDICINE



**DEVELOPMENT OF A SIMPLE PROGNOSTIC SCORE
FOR PREDICTING IN-PATIENT DEATH IN CHILDREN
WITH SEVERE ACUTE MALNUTRITION**

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STATEMENT OF AUTHOR'S ROLE

My role in this project included:

- Patient recruitment, patient care and data collection
- Formulated the study questions with input from my supervisor and the study PI
- Obtained ethics approval from the LSHTM
- Conducted literature review and identified variables used in the analysis
- recoded and re-categorised the variables
- wrote the analysis plan, performed statistical analyses and interpreted the results
- wrote the report

ABSTRACT

Introduction: Severe acute malnutrition (SAM) is a common cause of death and hospitalization in developing countries. Mortality remains high although treatment guidelines are capable of reducing mortality below 5%. It is important to identify high risk children and target care. Prognostic scores are used in patient care to predict the course of illness. A number of prognostic scores for children exist, but most are developed in high resource setting hence unsuitable for developing countries. Only a few prognostic indices exist for children with SAM and none has been validated.

Objectives: To develop and validate a simple scoring system for identifying children with SAM at high risk of dying.

Methods: Baseline clinical and laboratory data, obtained from 1200 children with SAM in a prospective cohort at Kilifi district hospital, Kenya was used. The outcome was all cause in-patient death. Variables known to be prognostic in SAM were used in a forward stepwise logistic regression model. Scores were developed from the coefficients of logistic regression. Two models were developed, a basic model with clinical variables only and a more complex model that included both clinical and laboratory variables.

Results: Weak pulse volume, sunken eyes, oedema, MUAC<10cm and mother's death were independent predictors of in-patient death in basic model. Hyponatremia, hypokalemia and Blantyre coma scale <5 and variables in the basic model except sunken eyes were independent predictors in the complex model. All models had good calibration. The complex model had better discrimination (area under ROC 0.77 vs. 0.66). The scores from the basic and complex models had good sensitivity (87% and 92% respectively) but poor specificity (33% and 32% respectively).

Conclusion: simple scores can be used to identify most of children at high risk of dying. The scores need to be prospectively validated in another setting before they can be used.

BACKGROUND

Malnutrition is a common cause of morbidity and mortality in developing countries. It is a risk factor for over 50% of the 11 million annual childhood deaths (1-2). Malnutrition may manifest as wasting (low weight for height), stunting (low height for age), underweight (low weight for age) or micronutrient deficiency. Whereas mild and moderate malnutrition are the most common and account for most of the deaths, nearly a quarter of deaths attributable to malnutrition are caused directly by severe acute malnutrition (SAM)(2).

Severe acute malnutrition (SAM) is defined as a weight for height measurement of 3 SD or more below mean or presence of bilateral pitting oedema or a mid upper arm circumference of <115mm (3). It is estimated that about 13 million children in developing countries have SAM. SAM is associated with 1.5 million deaths annually (2). Severe acute malnutrition is also a leading cause of hospital admission in some developing countries (4) and has a high case fatality, usually between 20-60% (5). Improving outcome in severe malnutrition is therefore essential in achieving the millennium development goals.

The World Health Organization (WHO) guidelines for the management of patients with severe malnutrition aim to reduce the case fatality rate to between 1-5% (6). These guidelines follow a series of steps. The initial steps involve identification and management of life threatening complications. The guidelines recognize hypoglycaemia, hypothermia, dehydration and septic shock as the most common and critical complications. Children also receive special milk diet and micronutrient supplementation for nutritional rehabilitation. It is recognized that most children with SAM have concomitant infections (7-9). Therefore all children are started on oral or parenteral antibiotics. Despite existence of these guidelines for over 2 decades, most hospitals have not managed to attain the low case fatality rate envisaged.

The outcome of patient care depends on the quality of care given to the patient and the severity of illness. A number of studies have attributed the poor outcome in SAM to sub-optimal nursing and clinical care due to inadequate training(5). However, quality of care in most hospitals in developing countries is limited by lack of resources (10). In Malawi, it was shown that establishing a good triage system can reduce all cause mortality in children in developing countries despite resource limitation (11). Therefore, identifying high risk children at the time of admission so that appropriate intervention can be initiated at an early stage, may prevent deaths in SAM.

A number of risk assessment tools have been developed for children. In the WHO guidelines, individual danger signs, namely shock, severe anaemia, hypothermia, hypoglycaemia and dehydration are used to identify high risk children. These signs have however been criticized as not sensitive enough (12-13). Prognostic scores have been in use in patient care for a long time. They are derived from statistical models that combine data from a patient to predict the course of illness in that patient. They are well accepted as good aids in clinical decision making and have been shown to be more accurate than clinical prediction (ref). They have been used in acute and chronic conditions in children. They serve a number of purposes. They guide the patient and clinician on the likely outcomes of her disease and can be used for ordering additional tests or choosing treatment. They are also useful in designing clinical trials where they can be used for stratification or test for differential therapeutic benefit. A well developed and validated score would be helpful in triage of children with SAM as well as in research on clinical care of SAM in developing countries.

There are a number of prognostic scores used in children. These include Paediatric risk of mortality (PRISM) score(14), Paediatric Index of Mortality score (15) and Paediatric Multiple Organ Dysfunction Score (P-MODS)(16). These scores are designed for use in critically ill children. They require intensive monitoring and laboratory tests and are unsuitable for routine use in poor resource settings. Moreover, none of them were specifically designed for use in SAM.

LITERATURE REVIEW

SEARCH STRATEGY

A good prognostic score should be accurate in predicting survival or death but still be simple to use at the bedside. This involves use of strong and accurate prognostic indicators. To the best of my knowledge, there has not been a systematic review of prognostic indicators in SAM. A literature search was therefore conducted electronically using the PUBMED database. The objective was to identify prognostic indicators and prognostic scores for death in SAM in developing countries. The search was limited to articles in English or where an English translation of the abstract was available. The search terms used include; "(child OR children OR infant) AND (death OR mortality OR outcome) AND (risk factor OR prognos* OR predict*) AND (malnutrition OR malnourished OR undernourished OR underweight) AND (africa* OR developing countr* OR low income countr*)".

RESULTS

Four hundred and three articles were identified. The title and abstract of each article were examined to identify suitable references. Full text articles were sought and where lacking, information extracted from the available abstract. Articles that were excluded related to malnutrition as a risk factors for childhood mortality (194), risk factors protein energy malnutrition (44), maternal nutrition and health (79), neonatal nutrition and health (20), obesity(7) or review articles of nutrition physiology or policy(56). Fifteen articles were identified which involved studies that sought to identify prognostic indicators of severe malnutrition. Table 1 summarizes the findings.

The definition of severe malnutrition varied across the studies. Older studies included a WHZ score of -2 or WAZ score in defining severe malnutrition. There are inconsistencies in the cut-off used in anthropometric measures. For example, while Bitwe et al (17) used a MUAC cut-off of 115mm, Dramaix et al (18-19) adopted three categories; >125 mm, 115-124mm and <115 mm. Despite this, anthropometric markers namely WHZ score (20-21), MUAC (17-18, 20, 22), WAZ score (17, 21-22) and oedema (19, 23-24) have been found to be prognostic. Other prognostic indicators identified in more than one study include infection (5, 17, 23), impaired consciousness (12, 17), hypoglycaemia (5, 12), hyponatremia and hypokalemia (12, 21), hypoalbuminaemia (19, 21, 25), and dehydration (12, 22). There is inconsistency in the prognostic ability of gender and age. Although some signs e.g. haemoglobin level, malaria parasitemia, tachycardia and hepatomegally, are of prognostic value in well nourished children, they have been found to be of no value in SAM.

Only a few prognostic indices have been developed for children with SAM. The Prudhon Index (26) predicts the number of children likely to die and is used to assess the quality of care in therapeutic feeding centres. TFC are used to manage children without complications and have lower mortality rates. Moreover, the score doesn't predict the risk in an individual child. A study conducted in Kenya, stratified children into 3 risk groups based on their clinical findings (12). High risk symptoms included depressed conscious state, bradycardia, features of shock and hypoglycaemia. Children with any of these symptoms had case fatality rate of 34%. A score developed in central Africa identified age below 12 months, MUAC <115 mm, impaired consciousness, malaria, bacteraemia and other infections other than gastroenteritis or respiratory infection in the score(17). The score varied between 0 and 10 and had good discrimination with area under ROC of 0.8. However, none of these indices have been validated.

Table 1: Summary of studies of prognostic indicators in severe malnutrition from literature review

Author	Setting	Period	Study Design	Inclusion Criteria	% death	Sample size	Risk Factors		No Association
							Univariable	Multivariable	
1. Sunguya B	Hospital - Kenya, Tanzania		?cohort ?prospective	Not given- abstract only	28% and 19%	1121	Oedema Sepsis	Not done	
2. Savadogo L	Nutrition centre - Burkina Faso-	1999-2003	Cohort ?Retro/?Prosp	Not given – Abstract only	16%	1322	WHZ <-4 Low MUAC for Age	WHZ MUAC for Age	
3. Maitland K	Hospital - Kenya	2000-2002	Retrospective	Visible severe wasting or WHZ<-3 or MUAC<11.5 or Symmetrical oedema	19%	920	Marasmus, Weak pulse Impaired consciousness, Hypoxia Acidotic respiration, Bradycardia Capillary refill, Temperature gradient, Lethargy , Hypoglycaemia, Hyponatremia Base deficit >-10, Hypokalemia Dehydration	Impaired Consc Bradycardia CRT>2sec, temp gradient, weak pulse vol Hypoglycaemia Deep breathing sunken eyes reduced skin turgor Lethargy Hyponatremia hypokalemia	Hb WBC count Malaria Tachycardia
4. Bachou H	Hospital - Uganda	Sept 2003 - Nov 2003		WHZ <-3 and/or presence of oedema	24%	220	Hypokalemia Hypoalbuminemia Transfusion, IV infusion Hypothermia , Hyponatremia, HIV Diarrhoea	Transfusion IV infusion	Sex, age group Oedema Malaria
5. Bitwe R	DRC - hospital	1.4.2003 to 31.3.2004	prospective				Age, WAZ, MUAC BCS, Neck stiffness Indrawing, Infection	Age<12m, WAZ MUAC<11.5 Impaired Consciousness Bloodstream infection	

6. Bahwere P	Central Africa		Prospective	Children with LRTI SAM- oedema			Girls WHZ < or = -3 serum albumin <16 g/l		
7. Schofield C	South Africa		Prospective Interventional				sepsis hypoglycemia		
8. Manary MJ	Malawi			Kwashiorkor	26%	68	Hypophosphatemia (<1.0 mg/dL)		
9. Gernaat HB	Zambia	1987 and March 1989	Prospective	Wellcome classification(WHZ ≤-2 and/or edema)	25.8	299	Dehydration, Pneumonia Stunting, MUAC<104		
10. Dramaix M 1993	Zaire	1986 to 1988	Prospective	Waterlow classification	17.4%	1129(75 % PEM)	edema arm circumference, serum albumin transthyretin		
11. Dramaix M 1996	Zaire	Aug 1986 to Oct 1988	Prospective	Waterlow classification		1129	wasting MUAC < 125 mm serum albumin < 16 g/l oedema	serum albumin MUAC oedema	
12. Erinoso HO	Nigeria		Prospective		75% (<12mths), 33%(30- 36mths)	150	Age weight-for-age, weight- for-height MUAC Hypokalaemia Hyponatraemia hypoproteinaemia hypoalbuminaemia		Hepatomegaly
13. Friedland	South Africa					792	Bacteraemia		
14. Shann F	Papua New Guinea					748	No fever		
15. Ogbeide O	Nigeria	Jan1971 - Dec 1973 Oct1974 - Mar 1975			15.3%	196	Age Resp infection/measles kwashiorkor		

RATIONALE FOR THE STUDY

Severe malnutrition is common in developing countries and associated with high mortality rates. While most children with SAM can be managed in community based therapeutic centre, those with complications need to be identified and referred to the hospitals for medical care. Most of these children will be managed in facilities that have minimal resources and inadequate staffing. It is important to identify features in children with SAM that are likely to predict death so as to plan for care and target resources. At the same time, clinical trials are needed to improve outcome in management of SAM. This will require good knowledge of the prevalence and effect of treatable complications. There is a paucity of studies that have comprehensively assessed prognostic factors in children with SAM. Most of these have looked at individual risk factors. Of the few prognostic indices available, none of the prognostic indices developed have been prospectively validated.

AIM AND OBJECTIVES

The overall aim was to develop a system for identifying children admitted to hospitals with SAM who are at an increased risk of dying. The specific aims were;

- To identify baseline clinical and laboratory features that independently predict death in children with SAM.
- To develop and validate a simple prognostic score for death in children admitted to hospital with SAM using routinely collected clinical and laboratory data.

PATIENTS AND METHODS

STUDY SETTING

The study was conducted at the Kilifi District Hospital (KDH), a public health institution located in Kilifi district. The district is located along the Kenyan Coast. Kilifi District is among the poorest districts in Kenya and is a malaria endemic area. Most of the inhabitants are subsistence farmers (27). KDH serves a population of about 240,000 people, nearly 50% of whom are under 12 years. SAM is the fourth commonest cause of admission to the hospital, accounting for about 16 % of annual admissions to KDH (12).

STUDY POPULATION

The study recruited children who were admitted to the paediatric ward with features of SAM. The inclusion criteria were;

- Age \geq 6 months and $<$ 12 years

- Features of SAM defined as; Oedema of both feet (of nutritional origin) or Weight for height z score (WHZ) <-3(NCHS reference) or Mid upper arm circumference (MUAC) < 11cm.

Consent was obtained from the guardians or parents by ward based fieldworkers after explanation of the study procedures in the local language. Those who declined consent were excluded from the study but received standard care.

STUDY DESIGN

This was a prospective, hospital based cohort study which began in June 2005. This report includes data collected on admission from patients recruited by June 2009.

Data collection

All children were assessed on admission and their demographic, anthropometric and clinical data captures in a standardized electronic proforma (Appendix A). Demographic, anthropometric and vital signs details were collected by trained clinical assistants. The weighing scales were regularly calibrated while the temperature, heart rate and oxygen saturations were collected using digital instruments. All clinicians were trained in recognition of clinical signs using videos of clinical signs before the study started and had regular updates.

All children received a standardized package of laboratory investigation and care. Investigation done on admission included a malaria blood slide, complete blood count, blood culture and electrolytes. These were double entered into a computer database program (Filemaker Version 5, www.filemaker.com). Clinical management was according to the WHO guidelines for management of children with SAM (6). This includes; intravenous antibiotics (ampicillin and gentamicin), rehydration (usually oral with Rehydration solution for malnutrition (RESOMAL)). Nutritional rehabilitation was done using special milk diets (F75 and F100). All children were seen at least once daily by a clinician and twice daily by a clinical assistant who took their clinical observations.

Sample size

A total of 1200 patients were recruited into the study between June 2005 and June 2009. This was divided into two; a development dataset and a validation dataset. Using a 2:1 split as suggested by Harrell et al (28), the development set had 800 patients. Figure 1 gives the power of the study with varying prevalence and magnitude of effect. The development data set provides adequate power to identify a two fold increase in odds if the exposure prevalence is >5%; the type I error associated with this test being 0.05. Sample size calculation was carried out using PS: Power and Sample Size Calculation version 3.0 (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>)

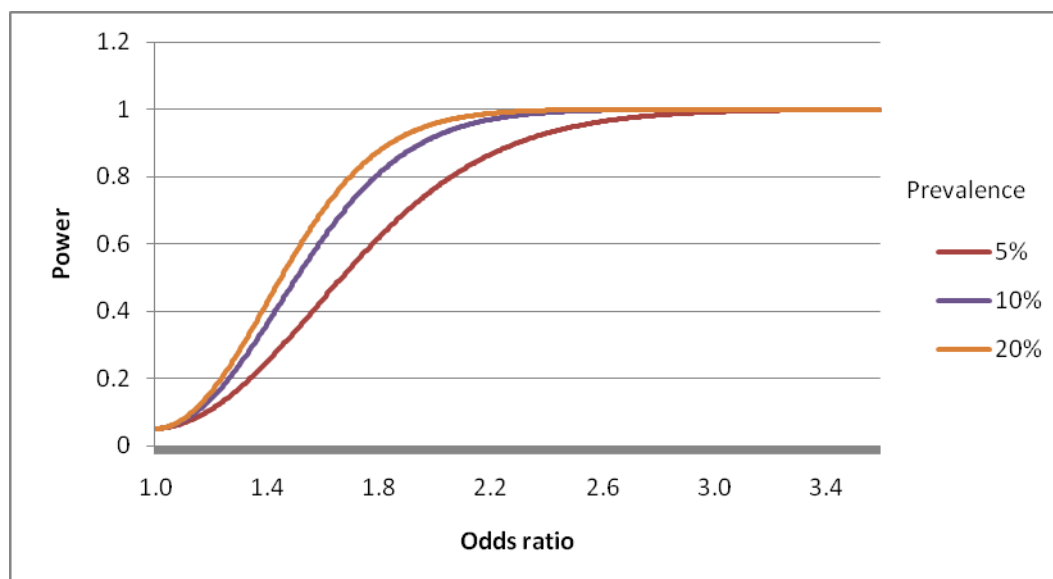


Figure 1: Power of the study against magnitude of effect given different prevalence of the predictor

OUTCOME

The final diagnosis was entered into a database either upon death or discharge. The outcome was all cause death before discharge from hospital. Those who absconded from hospital were classified as discharged alive. We only considered a single episode of hospitalization with SAM and those readmitted with SAM were excluded from the study.

CANDIDATE PREDICTORS

From all the variables that are routinely collected as part of the admission process, only those that have been identified as prognostic were considered. These included

- Demographic – age, sex, whether their mother is dead
- Anthropometric - MUAC, presence of oedema, WAZ
- Symptoms – history of acute diarrhoea
- Signs – heart rate, respiratory rate, oxygen saturation, temperature
- Examination finding – dehydration (sunken eyes, reduced skin turgor), indrawing, acidosis (deep breathing), level of consciousness (Blantyre coma scale, lethargy), shock (pulse volume temperature gradient, capillary refill time).
- Laboratory – random blood sugar, white blood cell count, serum potassium, serum sodium, HIV antibody status.

DATA CLEANING

All patients who were admitted to the ward and who fulfilled the inclusion criteria were considered. Comparisons of distribution of baseline characteristic between those recruited to the study and those who were not were made to determine if the two groups differed systematically from each other. After dropping those who were not recruited into the study,

variables were tabulated to identify missing observations. Scatter plots were done to identify outliers. All observations considered not clinically plausible were changed to missing. Patients with missing observations were classified into two; those missing clinical data only, those missing clinical and laboratory data. Each category was tabulated against the baseline characteristic and outcome to determine if those with missing observation differed from those with complete observations. Analysis was done on a complete case basis. Although complete case analysis leads to reduction in power and selection bias, imputation makes assumptions that did not hold in our data and was beyond the scope of this project (28-29).

DATA REDUCTION

Categorizing continuous variable results in loss of information and bias but results in models that are easier to use in a clinical setting (30). A prognostic score with continuous predictors may be practical in referral hospitals where computers are available but cannot be used in other settings. For this reason we developed two models, one using continuous variables and the second one with categorical variables. Categorization was done using cut-offs derived from either WHO guidelines (6) or Paediatric Advanced Life Support (PALS). Where no cut-offs were available, data was divided into quartiles and a nearest whole number used as a cut-off.

Assessing Linearity

The relationship between categorical variables and mortality was assessed graphically by plotting integer values of each variable against the log odds of death. Continuous variables were split into 10 categories and integer value of each category plotted against the log odds of death. Linearity and departure from linearity were assessed by adding quadratic terms into the model and doing likelihood ratio tests. Quadratic terms were used in the multivariable analysis if there was evidence that these terms improved the model fit.

Collinearity and Interactions

Variables are said to be collinear if there is an exact linear relationship between them. Such variables result in high P values or the wide confidence intervals on the regression coefficients, even when the variable is important. Only predictors that are likely to be correlated were considered and assessed by plotting scatter plots and calculating the correlation coefficient. If they were visually assessed as collinear or the correlation coefficient was more than 0.7, the most clinically sensible variable was chosen. Since the overall aim was to develop a simple score, only those variables in the final models where clinically plausible interactions were expected were considered. Specifically we considered interaction between oedema and any of the variables in the final model. This was explored with a likelihood ratio test (28). If there was good evidence of interaction between these variables, models were developed separately.

UNIVARIABLE ANALYSIS

Binary and categorical variables were presented as frequencies and percentages while continuous variables were presented as means \pm SD or median and inter-quartile range for normally and non-normally distributed data respectively. Baseline differences were determined by Chi square test, chi square test for trend and Fisher's exact test for categorical variables. Unpaired t test or Kruskal-Wallis test were used for continuous variables. A temporal data split was done to provide data for validation. A random split makes the two data sets as similar to each other as possible. While the prognostic models developed in this may perform very well in the internal validation they usually fail in external validation. A non random split provides an opportunity for temporal validation of the model (31). Univariable association between each candidate predictor and in-patient mortality was assessed by means of Mantel Haenszel method and results described in odds ratio and 95% confidence interval.

MODEL BUILDING

Since the outcome was binary and the main interest was in occurrence of the outcome rather than time to outcome, logistic regression was used for model building. Two models were developed, a basic model included only clinical variables (Clinical-only model) and a more complex model included laboratory variables in addition to the clinical variables (Clinical+Laboratory model). For each model, two separate models were developed, one using continuous variables and a second with categorical variables. All variables in univariable analysis were included in the multivariable logistic regression model since all had previously been associated with mortality in SAM. A forward stepwise method of variable selection was adopted. Variables were added to the model in descending order of magnitude of association with in-patient death, described by the odds ratio. For each predictor added, we compared model fit using a likelihood ratio test. Variables that still had good evidence of association with in-patient death were retained in the model. Whereas a full model, incorporating all candidate predictors, is superior and avoids selection bias, it results in retention of unimportant variables (32).

Model performance

Model performance was assessed in terms of calibration and discrimination(31). Discrimination refers to the ability of the model to separate patients with different responses. Calibration compares the observed events and the predicted events when the study population is divided into groups. Calibration was assessed using the Hosmer-Lemeshow test. If the observed proportion of events agrees with the predicted probabilities, then the slope of the graph is 1. Discrimination was assessed using the area under receiver operator curve (ROC). A ROC is a graph of sensitivity versus one minus specificity as the cut-off is

varied (33-34). The area beneath the curve is used as a measure of the predictive power. A model with no predictive power has area ≤ 0.5 ; a perfect model has area 1. Calibration and discrimination was assessed on the development and on the validation dataset.

Score Development

The final models were presented as scores based on the regression coefficients in the logistic regression model. In the continuous model, the coefficients from the final model were used to calculate the probability of death, which was converted into a score. In the categorical models, the coefficients were divided by a common number to obtain a whole number that represented the score. The scores were applied to the validation dataset to describe the accuracy of the scores in predicting mortality at different cut-offs. Case fatality rate in patients within each score category was calculated and the accuracy of the score was described as sensitivity, specificity, positive predictive value and negative predictive value. Data analysis was done using Stata version 11.

Ethical Approval

The study was approved by Kenya Medical Research Institute national Ethical review Committee (SSC No. 927) and the ethics review committee of the London School of Hygiene & Tropical Medicine (April 2010)

RESULTS

PATIENT CHARACTERISTICS

During the study period, 17688 children were admitted into the paediatric ward of KDH, of whom 2045 (11.6%) had severe acute malnutrition. Twelve hundred (58.7%) of the children with SAM were recruited into the study. Table 2 shows baseline differences between those recruited into the study and those not recruited. Those who were not recruited were younger (median age 19 vs. 21 months) and had better anthropometric features namely; fewer had oedema (25% vs. 37.6%) or were underweight (mean WAZ score -3.2 vs. -4.0) and had higher MUAC (mean MUAC 12 vs. 11.1cm). They had a slightly lower case fatality (13.5% vs. 16.1%) and were less likely to have acidotic breathing pattern. A higher proportion of those not recruited had impaired consciousness, features of shock (weak pulse, delayed capillary refill time), electrolyte imbalance and chest wall indrawing compared to those who were recruited. Children who were recruited were more likely to have had a HIV antibody test done and among those tested more likely to be positive compared to those not recruited into the study. There was no difference in sex distribution between the two groups.

Table 2: Patients characteristics, comparing those enrolled into the study and those not enrolled into the study (n=2045)

Characteristic	Measure/	Not Recruited	Recruited	P value
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	category	No.	%	No.	%	
Discharge outcome	Alive	731	86.5%	1007	83.9%	
	Dead	114	13.5%	193	16.1%	0.106
Age in months	Median	19	10, 38 [≠]	21	15,33	<0.001
MUAC in cm	Mean	12	2.2 [†]	11.1	1.6	<0.001
Heart Rate(beats/minute)	Mean	148.8	28.8 [†]	144.1	27	<0.001
Respiratory rate (/minute)	Median	38	30, 48 [≠]	34	29, 42	<0.001
Oxygen saturation (%)	Median	99	95, 100 [≠]	99	97, 100	0.001
Blood glucose(mmol/L)	Mean	4.8	2.1 [†]	4.5	2	0.001
White blood cell count(x10 ⁶ /L)	Median	13	9.2, 19.3 [≠]	13	9.2, 18	0.410
Potassium(mmol/L)	Mean	3.7	1.1 [†]	3.3	1	<0.001
Sodium(mmol/L)	Mean	134.4	6.7 [†]	133	5.8	<0.001
Temperature(⁰ C)	Mean	37.7	1.2 [†]	37.5	1	<0.001
Weight for age Z score	Mean	-3.2	1.4 [†]	-4	1.1	<0.001
Sex	Female	378	44.7%	570	47.5%	
	Male	467	55.3%	630	52.5%	0.217
Oedema	Absent	633	75.0%	746	62.4%	
	present	211	25.0%	450	37.6%	<0.001
Temperature gradient	No	746	88.6%	1069	89.5%	
	Yes	96	11.4%	125	10.5%	0.505
Capillary refill time(sec)	1	411	48.8%	566	47.3%	
	2	350	41.5%	565	47.2%	
	3	82	9.7%	66	5.5%	<0.001 [‡]
Sunken eyes	No	665	78.8%	938	78.6%	
	Yes	179	21.2%	256	21.4%	0.900
Reduced skin turgor	No	690	81.8%	950	79.4%	
	Yes	154	18.2%	246	20.6%	0.193
Chest wall Indrawing	No	589	69.8%	984	82.2%	
	Yes	255	30.2%	213	17.8%	<0.001
Deep Breathing	No	728	86.3%	1110	85.6%	
	Yes	116	13.7%	187	14.4%	<0.001
Blantyre coma scale	0	15	1.8%	6	0.5%	
	1	18	2.1%	3	0.3%	
	2	25	3.0%	10	0.8%	
	3	28	3.3%	22	1.8%	
	4	73	8.7%	52	4.3%	
Lethargy	5	684	81.1%	1103	92.2%	<0.001 [‡]
	No	744	88.2%	1062	88.8%	
Impaired Consciousness	Yes	100	11.8%	134	11.2%	0.653
	No	742	87.9%	1148	96.0%	
Weak Pulse Volume	Yes	102	12.1%	48	4.0%	<0.001
	No	773	91.7%	1135	94.9%	
Mother Dead	Yes	70	8.3%	61	5.1%	0.004
	No	819	97.4%	1154	96.3%	
	Yes	22	2.6%	44	3.7%	0.184

History of acute diarrhoea	No	569	67.4%	759	63.8%	0.090
	Yes	275	32.6%	431	36.2%	
HIV antibody test Status	Negative	423	58.0%	661	64.9%	<0.001‡
	Positive	80	11.0%	206	20.2%	
	Not tested	226	31.0%	152	14.9%	

‡inter-quartile range †standard deviation ‡Score test for trend of odds, MUAC (Mid Upper Arm Circumference)

Forty eight percent of study participants were boys while the median age was 21 months. Median duration of hospitalisation was 11 days (IQR 8-18). Those discharged alive had a median duration of 12 days (IQR 8-19) while those who died were hospitalised for a median duration of 7 days (IQR 3-11). Sixty one children (5% of study participants) had some clinical data missing and were excluded from the analysis. Laboratory data was missing from 285(23.8%) of the participants. Clinical characteristics were similar between those with and without missing laboratory data (Table 3) except for temperature gradient, which was less common in those with missing laboratory data. In addition, those with missing data had a slightly lower case fatality rate compared to those with complete laboratory data (13.3% vs. 16.9%)

Table 3: Characteristics of patients enrolled into the study, comparing those with complete laboratory data and those with missing laboratory data (n=1200)

Characteristic	Measure/ category	Not Missing		Missing Lab		P value
		No.	%	No.	%	
Discharge outcome	Alive	760	83.1%	247	86.7%	0.148
	Dead	155	16.9%	38	13.3%	
Age in months	Median	21	15, 32‡	21	14, 35‡	0.975
MUAC in cm	Mean	11	1.6†	11.2	1.6†	0.103
Heart Rate(beats/minute)	Mean	144.9	26.7†	141.3	27.6†	0.048
Respiratory rate (/minute)	Median	34	28, 42‡	35.5	30, 42‡	0.201
Oxygen saturation (%)	Median	99	96, 100‡	99	97, 100‡	0.856
Temperature(°C)	Mean	37.5	1†	37.5	1†	0.985
Weight for age Z score	Mean	-4	1.1†	-4	1.1†	0.409
Sex	Female	436	47.7%	134	47.0%	0.852
	Male	479	52.3%	151	53.0%	
Oedema	Absent	562	61.6%	184	65.0%	0.293
	present	351	38.4%	99	35.0%	
Temperature gradient	No	806	88.3%	263	93.6%	0.011
	Yes	107	11.7%	18	6.4%	
Capillary refill time(sec)	1	433	47.4%	133	47.0%	0.972‡
	2	430	47.0%	135	47.7%	
	3	51	5.6%	15	5.3%	
Sunken eyes	No	704	77.3%	234	82.7%	

	Yes	207	22.7%	49	17.3%	0.053
Reduced skin turgor	No	718	78.6%	232	82.0%	
	Yes	195	21.4%	51	18.0%	0.225
Chest wall Indrawing	No	752	82.3%	232	82.0%	
	Yes	162	17.7%	51	18.0%	0.909
Deep Breathing	No	842	92.1%	268	94.7%	
	Yes	72	7.9%	15	5.3%	0.145
Blantyre coma scale	0	5	0.5%	1	0.4%	
	1	3	0.3%	0	0.0%	
	2	9	1.0%	1	0.4%	
	3	15	1.6%	7	2.5%	
	4	41	4.5%	11	3.9%	
	5	840	92.0%	263	92.9%	0.679‡
Lethargy	No	808	88.5%	254	89.8%	
	Yes	105	11.5%	29	10.2%	0.559
Impaired Consciousness	No	874	95.7%	274	96.8%	
	Yes	39	4.3%	9	3.2%	0.414
Weak Pulse Volume	No	865	94.6%	270	95.7%	
	Yes	49	5.4%	12	4.3%	0.461
Mother Dead	No	886	96.8%	268	94.7%	
	Yes	29	3.2%	15	5.3%	0.096
History of acute diarrhoea	No	576	63.4%	183	64.9%	
	Yes	332	36.6%	99	35.1%	0.656

‡inter-quartile range †standard deviation ‡Score test for trend of odds

Data splitting resulted in 783(69%) children in the development set and consisted of children admitted before 1st January 2008. Mortality was higher in the development set compared to the validation set (17.9% vs. 11.0%, P=0.003). Differences between the validation and development set are shown in table 4. The proportion of children with respiratory symptoms (chest wall indrawing, high respiratory rate), temperature gradient or tested for HIV was lower validation dataset. There was an increase in the mean oxygen saturations and a decrease in mean blood glucose.

Table 4: Clinical and laboratory characteristics of children with SAM, comparing the development and validation dataset (n=1200)

Characteristic	Measure/ category	Validation Set		Development Set		P value
		No.	%	No.	%	
Discharge outcome	Alive	317	89.0%	643	82.1%	
	Dead	39	11.0%	140	17.9%	0.003
Age in months	Median	21	14,34‡	21	15,32‡	0.359
MUAC in cm	Mean	11.1	1.6†	11.1	1.6†	0.806
Heart Rate(beats/minute)	Mean	143.5	27†	144	27†	0.562

Respiratory rate (/minute)	Median	36	31, 44 [‡]	34	28, 42 [‡]	<0.001	
Oxygen saturation (%)	Median	100	98, 100 [‡]	99	96, 100 [‡]	<0.001	
Blood glucose(mmol/L)	Mean	4.1	2 [†]	4.6	1.9 [†]	<0.001	
White blood cell count(x10 ⁻⁶)	Median	13.4	9.8, 17.7 [‡]	13	9.1, 18.4 [‡]	0.573	
Potassium(mmol/L)	Mean	3.3	1 [†]	3.3	1 [†]	0.962	
Sodium(mmol/L)	Mean	132.7	5.7 [†]	133.1	5.8 [†]	0.248	
Temperature(°C)	Mean	37.5	1 [†]	37.5	1 [†]	0.827	
Weight for age Z score	Mean	-4	1.1 [†]	-4	1.1 [†]	0.819	
Sex	Female	168	47.2%	369	47.1%		
	Male	188	52.8%	414	52.9%	0.984	
Oedema	Absent	218	61.2%	493	63.0%		
	present	138	38.8%	290	37.0%	0.577	
Temperature gradient	No	330	92.7%	693	88.5%		
	Yes	26	7.3%	90	11.5%	0.030	
Capillary refill time(sec)	1	194	54.5%	344	43.9%		
	2	147	41.3%	390	49.8%		
	3	15	4.2%	49	6.3%	<0.001 [‡]	
Sunken eyes	No	287	80.6%	612	78.2%		
	Yes	69	19.4%	171	21.8%	0.346	
Reduced skin turgor	No	300	84.3%	607	77.5%		
	Yes	56	15.7%	176	22.5%	0.009	
Chest wall Indrawing	No	280	78.7%	658	84.0%		
	Yes	76	21.3%	125	16.0%	0.027	
Deep Breathing	No	328	92.1%	728	93.0%		
	Yes	28	7.9%	55	7.0%	0.613	
Blantyre coma scale	0	2	0.6%	3	0.4%		
	1	0	0.0%	2	0.3%		
	2	3	0.8%	6	0.8%		
	3	5	1.4%	12	1.5%		
	4	24	6.7%	21	2.7%		
	5	322	90.4%	739	94.4%	0.260 [‡]	
	Lethargy	No	312	87.6%	707	90.3%	
	Yes	44	12.4%	76	9.7%	0.176	
	Impaired Consciousness	No	343	96.3%	755	96.4%	
		Yes	13	3.7%	28	3.6%	0.949
Weak Pulse Volume	No	345	96.9%	743	94.9%		
	Yes	11	3.1%	40	5.1%	0.127	
Mother Dead	No	349	98.0%	750	95.8%		
	Yes	7	2.0%	33	4.2%	0.056	
History of acute diarrhoea	No	236	66.3%	489	62.5%		
	Yes	120	33.7%	294	37.5%	0.212	
HIV antibody test Status	Negative	163	72.1%	496	63.3%		
	Positive	48	21.2%	153	19.5%		
	Not tested	15	6.6%	134	17.1%	<0.001 [‡]	

[‡]inter-quartile range [†]standard deviation [‡]Score test for trend of odds

ASSUMPTION TESTING

The association between in-patient death and Blantyre coma scale and capillary refill time were best described as linear terms and were analysed as such in multivariable analysis. Figure 2 shows a plot of change in log odds of death and unit change in each of the variables.

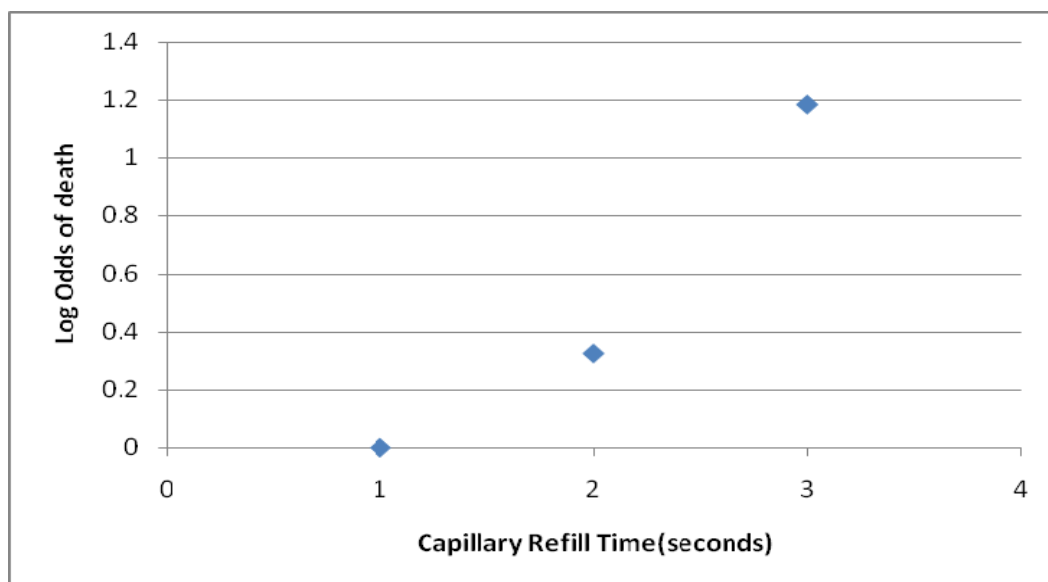
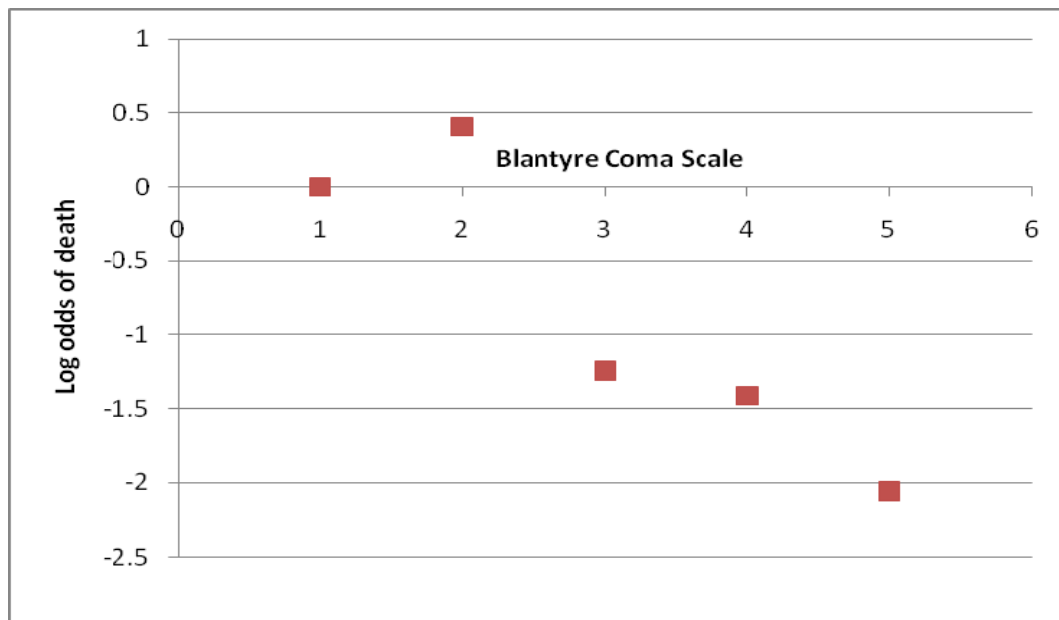


Figure 2: Relationship between BCS, Capillary refill and Log odds of death

There was strong evidence that a quadratic relationship best described the association between in-patient death and serum potassium (LRT Chi=16.43 P<0.001) and blood glucose

(LRT chi =10.28 P=0.001). There was weak evidence for a quadratic relationship with MUAC (LRT chi= 2.77 p=0.097) and sodium (LRT chi 3.23 p=0.072) and the association was thus described in linear terms. Other continuous variables, namely respiratory rate, heart rate, age, white cell count were best described by a linear relation.

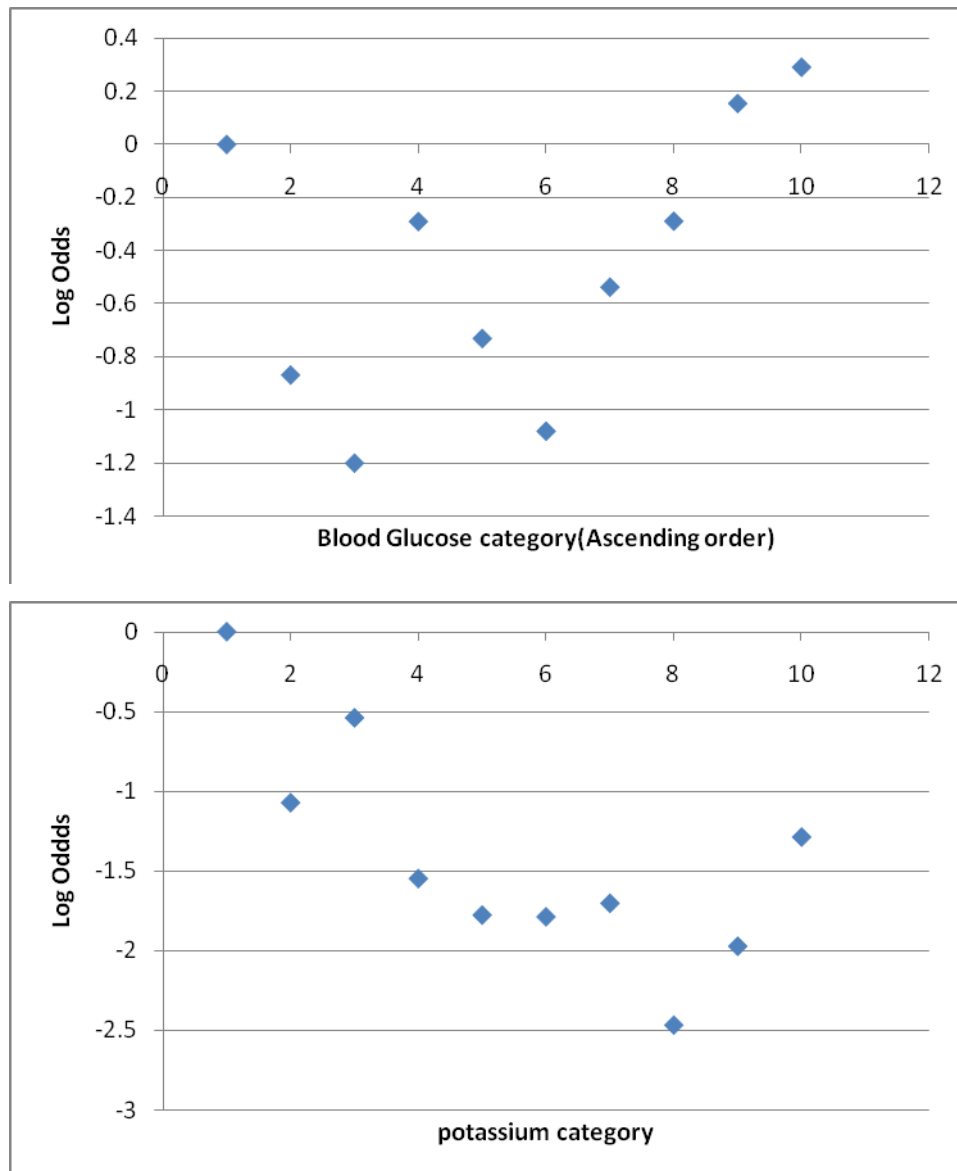


Figure 3: Relationship between Blood glucose, Serum potassium and Log odds of death

CATEGORIZATION

Axillary temperature, heart rate, blood glucose, white blood cell count, serum potassium and sodium were categorized into 3 categories; low, normal and high levels according to the past literature. Only a few participants had low temperature (n=4), high serum sodium (n=8), high blood glucose (n=6), high serum potassium (n=9). These observations were classified in the normal category for each of the variables. Capillary refill time and respiratory rate were categorized into two according to the Paediatric Advanced Life Support (PALS) and WHO

guidelines respectively. Age, MUAC and weight for age Z score were categorized into quartiles.

UNIVARIABLE ANALYSIS

Table 5 shows the univariable association between each of the variables and in-patient mortality. MUAC (OR 0.82 95%CI 0.73, 0.91 P<0.001), weight for age Z score (OR 0.83 95% CI 0.71, 0.98 P=0.029) heart rate (OR 0.99 95%CI 0.98, 0.99 P<0.001), oxygen saturation (OR 0.96 95%CI 0.94, 0.98 P<0.001), axillary temperature (OR 0.73 95%CI 0.61, 0.88 P<0.001) and Blantyre coma scale (score for trend p<0.001) were inversely associated with in-patient death. Having sunken eyes, reduced skin turgor, weak pulse volume, acidotic respirations were also strongly associated with in-patient death. Presence of oedema was associated with an increase in the odds of in-patient death although the confidence intervals included 1 (OR 1.35 95% CI 0.93, 1.95 p=0.116). Other variables not associated with in-patient death in the univariable analysis include sex, age, respiratory rate, history of diarrhoea and chest wall indrawing. All laboratory variables except white blood cell count were associated with in-patient death. Upon categorization, MUAC, weight for age Z score serum sodium, serum potassium, capillary refill time, heart rate Blantyre coma scale and oxygen saturation were still strongly associated with in-patient death. Axillary temperature, white blood cell count had weak association with in-patient death. Age and respiratory rate were not associated with in-patient death.

Table 5: Univariable analysis of clinical and laboratory predictors of in-patient death in children with SAM (n=783)

Characteristic	Measure/category	Odds ratio	95% CI		P Value [†]
Sex	Female	1.00			
	Male	0.96	0.67	1.39	0.849
Age in months	months	1.00	0.99	1.01	0.907
Oedema	Absent	1.00			
	present	1.35	0.93	1.95	0.116
MUAC in cm	Mm	0.82	0.73	0.91	<0.001
Heart Rate	Beats/min	0.99	0.98	0.99	<0.001
Respiratory rate	Breaths/min	1.01	0.99	1.02	0.406
Oxygen saturation	%	0.96	0.94	0.98	<0.001
Temperature	°C	0.73	0.61	0.88	<0.001
Weight for age	Z score	0.83	0.71	0.98	0.029
Temperature Gradient	No	1.00			
	Yes	1.81	1.09	3.01	0.021
Capillary refill time (sec)	1	1.00			
	2	1.43	0.97	2.13	
	3	2.92	1.48	5.76	0.002‡

Sunken Eyes	No	1.00			
	Yes	2.12	1.41	3.17	<0.001
Reduced Skin Turgor	No	1.00			
	Yes	1.85	1.23	2.78	0.003
Chest wall Indrawing	No	1.00			
	Yes	0.98	0.59	1.61	0.929
Deep Breathing	No	1.00			
	Yes	2.65	1.46	4.79	<0.001
Blantyre coma scale	2	1.00			
	3	0.11	0.01	1.11	
	4	0.23	0.04	1.22	
	5	0.12	0.03	0.41	<0.001‡
Lethargy	No	1.00			
	Yes	2.19	1.29	3.72	0.003
Impaired Consciousness	No	1.00			
	Yes	3.14	1.43	6.90	0.003
Weak Pulse Volume	No	1.00			
	Yes	4.16	2.15	8.07	<0.001
Mother Dead	No	1.00			
	Yes	3.65	1.77	7.52	<0.001
Acute Diarrhoea	No	1.00			
	Yes	1.36	0.94	1.97	0.105
Blood glucose	mmol/L	1.18	1.07	1.31	0.001
White blood cell count	X10 ⁻⁶ /L	1.00	0.98	1.02	0.836
Potassium	mmol/L	0.59	0.48	0.71	<0.001
Sodium	mmol/L	0.89	0.86	0.92	<0.001
HIV Status	Negative	1.00			
	Positive	1.78	1.14	2.80	
	Not tested	1.74	1.09	2.80	0.006‡
Weight for Age Z score	>-3	1.00			
	-3 - -3.9	0.96	0.53	1.75	
	-4 - -4.9	1.07	0.58	1.96	
	≤-5	1.96	1.05	3.65	0.0113‡
Tachypnoea	No	1.00			
	Yes	0.96	0.63	1.45	0.831
Tachycardia	No	1.00			
	Yes	0.64	0.43	0.95	0.025
MUAC(cm)	>12	1.00			
	11.1 - 12	0.92	0.50	1.67	
	10.1 - 12	0.99	0.55	0.77	
	<10	2.13	1.27	3.60	0.001‡
	Age(months)	<12	1.00		
	12-23	0.64	0.37	1.08	
	24 - 35	0.51	0.27	0.96	
	36 -49	0.67	0.34	1.32	

	>60	0.78	0.37	1.64	0.501‡
Hypoxia	No	1.00			
	Yes	2.43	1.21	4.87	0.010
Capillary refill time	<2 sec	1.00			
	>=2sec	1.57	1.07	2.31	0.019
Fever	No	1.00			
	Yes	0.71	0.48	1.03	0.069
White Blood cell count	Normal	1.00			
	Leucocytosis	1.35	0.92	1.98	
	Leucopenia	1.73	0.61	4.93	0.090‡
Hyponatremia	No	1.00			
	Yes	4.55	2.41	8.57	<0.001
Hypokalemia	No	1.00			
	Yes	3.51	2.28	5.38	<0.001
Hypoglycemia	No	1.00			
	Yes	2.42	1.20	4.84	0.010
Blantyre coma scale	5	1.00			
	<5	2.54	1.32	4.90	0.004

†Walds test(Null hypothesis=crude OR =1), ‡Score test for trend of odds, MUAC (Mid Upper Arm Circumference)

MULTI-VARIABLE ANALYSIS USING CONTINUOUS VARIABLES

All clinical variables were entered into the final logistic regression model in the order of their association. Weak pulse volume, presence of sunken eyes, MUAC, heart rate, having a deceased mother and presence of oedema were all independently associated with in-patient death (table 6). Increase in MUAC (OR 0.85 95% CI 0.75-0.96 P=0.009) and heart rate (OR 0.99 95% CI 0.98-1.00 P=0.005) were associated with a reduction in odds of in-patient death, while weak pulse volume (OR 2.81 95% CI 1.34-5.89 P=0.006), sunken eyes (OR 1.84 95% CI 1.15-2.94 P=0.011), having a dead mother (OR 3.61 95% CI 1.66-7.87 P=0.001) and presence of oedema (OR 1.84 95% CI 1.21-2.81 P=0.005) were associated with an increase in the odds of in-patient death. There was weak evidence for an inverse association between oxygen saturation and in-patient death (OR 0.98 95% CI 0.96-1.00 P=0.094)

When laboratory variables were used, serum sodium, potassium, blood glucose, having a deceased mother, MUAC oxygen saturation and presence of were all strong independent predictors of death (table 6). An increase in serum sodium was associated with a decrease in odds of in-patient death (OR 0.91 95% CI 0.88-0.95 P<0.001). MUAC, presence of oedema, oxygen saturation and having a deceased mother were still independent predictors of in-patient death. However, this resulted in heart rate, sunken eyes and weak pulse volume being dropped from the model as their OR were attenuated towards one in the multivariable

model. There was no evidence for interaction between oedema and any of the variables in the final model.

Table 6: Multivariable predictive model using continuous variables to predict in-hospital death in SAM

Variable	Category/ measure	Clinical Only model				Clinical + Laboratory model			
		Odds Ratio	95 % CI		P value†	Odds Ratio	95 % CI		P value†
Mother Dead	No	1.00				1.00			
	Yes	3.61	1.66	7.87	0.001	2.54	0.92	7.06	0.073
Oedema	No	1.00				1.00			
	Yes	1.84	1.21	2.81	0.005	1.91	1.19	3.09	0.008
MUAC	cm	0.85	0.75	0.96	0.009	0.81	0.70	0.94	0.006
Oxygen saturation	%	0.98	0.96	1.00	0.094	0.98	0.96	1.00	0.047
Weak pulse volume	No	1.00							
	Yes	2.81	1.34	5.89	0.006				
Sunken eyes	No	1.00							
	Yes	1.84	1.15	2.94	0.011				
Heart rate	Beats/min	0.99	0.98	1.00	0.005				
Serum potassium	mmol/L					0.28	0.12	0.70	0.006
Potassium ²	mmol/L					1.15	1.00	1.31	0.050
Blood glucose	mmol/L					0.58	0.35	0.97	0.039
Blood glucose ²	mmol/L					1.06	1.01	1.12	0.012
Serum sodium	mmol/L					0.91	0.88	0.95	0.000

† Wald test (Null hypothesis - the adjusted OR=1)

MULTI-VARIABLE ANALYSIS USING CATEGORICAL VARIABLES

Weak pulse volume, having a deceased mother, MUAC, presence of oedema and sunken eyes were all retained as independent predictors of in-patient death. Weak pulse volume and having a deceased mother were associated with a more than 3 fold increase in the odds of in-patient death while children with oedema or sunken eyes had a two-fold increase in the odds of in-patient death. Heart rate which was an independent predictor as a continuous variable lost its association when categorized.

When laboratory variables were included in the model, seven variables were independently associated with in-patient death. Hypokalemia and hyponatremia were associated with a threefold increase in the odds of in-patient of death. Other predictors are shown on table 7. There was weak evidence for an association between in-patient death and weak pulse volume or Blantyre coma scale. There was no evidence for interaction between oedema and any of the variables in the final model.

Table 7: Multivariable predictive model using categorical variables to predict in-hospital death in SAM

Variable	Category /measure	Clinical findings model			Clinical + Laboratory model				
		Odds Ratio	95 % CI		P value	Odds Ratio	95 % CI		P value
Weak pulse volume	No								
	Yes	3.39	1.67	6.88	0.001	2.20	0.94	5.14	0.069
Mother dead	No								
	Yes	3.68	1.72	7.89	0.001	2.81	1.05	7.54	0.040
Sunken eyes	No								
	Yes	1.90	1.19	3.03	0.007				
Oedema	No								
	Yes	1.96	1.30	2.98	0.001	1.80	1.13	2.87	0.013
MUAC	>12								
	11-12	0.87	0.47	1.61		0.78	0.38	1.61	
	10-11	1.00	0.55	1.81		0.85	0.41	1.74	
	<10	1.93	1.12	3.33	0.008‡	1.68	0.89	3.18	0.036‡
BCS	5								
	<5					2.51	1.00	6.28	0.050
Hyponatremia	No								
	Yes					3.11	1.57	6.15	0.001
Hypokalemia	No								
	Yes					3.24	2.05	5.14	<0.001

‡likelihood ratio test, MUAC (Mid upper arm circumference), BCS (Blantyre coma scale)

MODEL PERFORMANCE

All models had good calibration in both development and validation datasets (table 8) except for the clinical-only model in the validation dataset (Hosmer-Lemeshow test Chi 16.05 P=0.098). However, the discrimination varied. Overall, inclusion of laboratory variables resulted in improvement in discrimination in both the continuous and categorical model (Area under ROC 0.76 vs. 0.66 and 0.77 vs. 0.66 respectively). There was no difference in discrimination between the categorical and continuous models and therefore the final score was developed using the categorical model.

Table 8: Calibration and discrimination of the models of predictors of in-hospital death in SAM

	Clinical –only Model		Clinical+ Laboratory model		
	Development	Validation	Development	Validation	
Continuous Model					
Hosmer-Lemeshow test	Chi	6.52	16.05	9.99	13.12
	P	0.5897	0.0982	0.27	0.22
Area under ROC		0.7037	0.6568	0.77	0.76

Categorical Model					
Hosmer-Lemeshow test	Chi	7.61	12.85	5.51	14.01
	P	0.3684	0.1171	0.7024	0.1727
Area under ROC		0.6749	0.6645	0.7511	0.7726

SCORE DEVELOPMENT

The coefficient was divided by 0.6 and 1.0 for the clinical finding and clinical + lab model respectively to derive the score, giving highest score of 7 and 12 respectively. Table 9 shows the scoring system derived from the multivariable model.

Table 9: Final risk score model of the predictors of in-patient death in SAM

Variable	Category	Clinical-only model		Clinical+Laboratory model	
		Coefficient	Score	Coefficient	Score
Weak pulse volume	No	0	0	0	0
	Yes	1.22	2	0.79	2
Mother dead	No	0	0	0	0
	Yes	1.30	2	1.03	2
Sunken eyes	No	0	0		
	Yes	0.64	1		
Oedema	No	0	0	0	0
	Yes	0.68	1	0.59	1
MUAC(cm)	>12	0	0	0	0
	11-12	-0.14	0	-0.25	0
	10-11	0.00	0	-0.17	0
	<10	0.66	1	0.52	1
Hyponatremia	No			0	0
	Yes			1.13	2
Hypokalemia	No			0	0
	Yes			1.18	2
Blantyre coma scale	5			0	0
	<5			0.92	2
Total Score			7		12

For comparison, the probability of dying was calculated using the equation derived from the each of the continuous models. The clinical model equation was; $P(\text{death}) = 1.65 + (\text{Weak pulse volume} \times 1.03) + (\text{Mother dead} \times 1.28) + (\text{Sunken eyes} \times .61) + (\text{Presence of oedema} \times .61) - (\text{MUAC} \times .17) - (\text{Oxygen saturation} \times .02) - (\text{Heart rate} \times .01)$. The Clinical+Laboratory model equation was; $P(\text{death}) = 16.81 + (\text{Mother dead} \times .93) + (\text{Potassium} \times .14) + (\text{Presence of oedema} \times .65) + (\text{blood glucose} \times 0.06) - (1.25 \times \text{Potassium}) - (0.53 \times \text{Blood Glucose}) - (\text{MUAC} \times .21) - (0.09 \times \text{Sodium}) - (0.02 \times \text{Oxygen saturations})$. Using different cut-offs, the scores were applied to the validation dataset and

the accuracy of the scoring system determined. Table 10 shows the results. Overall, the scoring system had very good sensitivity, but very poor specificity.

Table 10: Predictive accuracy of various scores for predicting in-patient death in SAM at different cut-offs

Model	Score	No. Of patients	No. Died	CFR	Sensitivity	Specificity	PPV†	NPV‡
Clinical only categorical	>=1	247	34	13.8%	87%	33%	14%	95%
	0	109	5	4.6%				
Clinical only categorical	>=2	63	16	25.4%	41%	85%	25%	92%
	<=1	293	23	7.8%				
Clinical +lab categorical	>=1	252	36	14.3%	92%	32%	14%	97%
	0	104	3	2.9%				
Clinical +lab categorical	>=2	128	25	19.5%	64%	68%	20%	94%
	<=1	228	14	6.1%				
Clinical only Continuous	>=1	273	33	12.1%	85%	24%	12%	93%
	0	83	6	7.2%				
Clinical only Continuous	>=2	85	16	18.8%	41%	78%	19%	92%
	<=1	271	23	8.5%				
Clinical +lab continuous	>=1	155	25	16.1%	83%	40%	16%	95%
	0	93	5	5.4%				
Clinical +lab continuous	>=2	64	19	29.7%	63%	79%	30%	94%
	<=1	184	11	6.0%				
Bitwe et al	>=1	246	36	14.6%	92%	34%	15%	97%
	0	110	3	2.7%				
Bitwe et al	>=2	234	34	14.5%	87%	37%	15%	96%
	<=1	122	5	4.1%				

‡Negative predictive power †Positive predictive Value

DISCUSSION

MAIN FINDINGS

Four models to predict death in children admitted to hospital with SAM have been developed using data routinely collected on admission. These models are suited for different health settings; a basic model that can be used in the community or poorly equipped health facilities and a more complex model that can be used in referral hospitals or centres with good laboratory facilities. The models have modest discrimination and good fit. Although the clinical+laboratory model has better discrimination than the clinical-only model, there was only a slight difference in the sensitivity of the scoring system derived. Discrimination did not differ between the categorical and the continuous models. This could be due to the fact that the relationship between most of the continuous variables and in-patient death was not linear. This is a great advantage since categorical models do not require much

computational skills and can easily be used at the bedside. Such models can be used in low income setting with the predictors losing little or no prognostic ability.

Weak pulse volume, presence of oedema, MUAC and losing a mother through death were independent predictors of in-patient death in both models. These predictors have been previously described as prognostic in this group of patients. MUAC, an anthropometric measure is a marker of severity of malnutrition. Severity of malnutrition has been described previously as an important predictor of death in SAM (35). A recent study showed that death of a mother was associated with a twenty five fold increase in the risk of death, with most deaths occurring due to malnutrition (36). It is postulated that this increased risk arises from interruption of breastfeeding, which is known to be protective against many respiratory and diarrhoeal infections (37). In this study, presence of oedema was associated with an increased risk of death. One previous study in the same setting had found oedema to be protective. However, this was conducted before the roll out of anti-retroviral therapy. HIV/AIDS usually present as marasmus and has had a big impact in the epidemiology of SAM (13).

Two laboratory features, hypokalemia and hyponatremia were found to be prognostic. A relevant observation was that inclusion of potassium and serum sodium in our models resulted in loss of the association between sunken eyes and death. Having sunken eyes is a sign of dehydration and severe dehydration usually results in electrolyte imbalance. Hypokalemia usually presents with muscular weakness, this might explain why lethargy does not appear prognostic in this study. It is not clear why Blantyre coma scale(BCS) is only prognostic in the laboratory model. Having a BCS less than 5 was rare and therefore due to sample size limitation could be a chance finding. Some features which had been previously described as prognostic are not in our model. Very few patients had some features e.g. bradycardia, hypoglycaemia, hypothermia, and therefore may be due to sample size limitation. It is also likely that these features are well recognized and better managed before referral to the hospital from dispensaries.

The scores have good sensitivity but very poor specificity. For a condition with very high mortality, this is good as one is able to identify most of the children who are at risk of dying. However, since SAM is common, the low specificity means that the score cannot reduce the hospital burden due to SAM. Notably, patient with a score of zero had case fatality rate of less than 5% in both scores. This CFR are within the acceptable range for children managed according to the WHO guidelines. However, they only comprise a third of the patients.

Comparison with previous studies

The scores compare well with previously developed score. When Bitwe et al (17) score was applied to our validation dataset, it had a sensitivity of 92%, similar to our laboratory score. The high sensitivity compared to the clinical score maybe because we used laboratory confirmed bacteraemia and malaria slides in the score. We did not also include the category “other infections” as it was not clear what infections were included. Most children seen in hospitals in developing countries do not have a diagnosis on admission while some present with multiple infections. It is therefore not prudent to include diagnosis in the score, but rather use clinical signs.

STRENGTHS AND LIMITATIONS

The prognostic scores were derived from data from a prospective observational study. This ensured that our data was accurate and devoid of any effect of an intervention as may be seen in scores derived from clinical trials data. The scores were also developed using multivariable techniques which ensured that the most predictive variables were obtained. The models were also internally validated with resulting good fit and discrimination. The scores performed well in a time period that had lower case fatality than the time period used to develop the scores. The two time periods also differed in prevalence of the predictors. It is said that temporal validation is usually superior to internal validation and performs close to external validation(31). The prognostic scores are also fairly accurate despite using simple clinical features.

The study has a number of limitations. First, the effect of selection bias on the results cannot be ignored. We excluded 5% of those recruited due to incomplete clinical observation while close to 25% were excluded from the laboratory model. This is however unlikely to have much effect on our estimates since those with missing observations did not differ from those with complete observations in outcome and in most predictors. Second, the results are less generalizable since our data was obtained only from one centre. In addition clinical characteristics of SAM patients included in the analysis differed from other SAM children not included in the analysis. This does not however affect the validity of the estimates obtained in the study. Moreover the case fatality of those included is similar to experiences in many hospitals in sub-Saharan Africa that in most published studies from different setting. Since the study only includes patients with SAM who were seen in hospital who may differ from those in the community, this may limit the use of the score to screen children in community based therapeutic centres.

Third, patients who received treatment which has an effect on the outcome and may also have been influenced by the presence of a prognostic indicator but treatment was not included in the model. For example the current guidelines recommend management of hypoglycaemia and hypothermia by oral or intravenous glucose correction and being kept

warm respectively This may have been adequately addressed and may explain why these features were not prognostic in our model. It would be unethical to withhold care. Moreover, our aim was to identify features that are not adequately addressed by the current guidelines.

The clinical and laboratory features used for our model were obtained on admission, which may reflect emergency interventions during admission or acute changes as a result of the travel to hospital or encounter with health care provider which may change after initial stabilization. In addition, characteristics at admission may not reflect changes that occur during hospitalization. Nosocomial infections are known to be a cause of death in children with SAM. However, the main aim was to produce a simple model that can be used to triage children on admission rather than characterize the changes during hospital stay, which may reflect the quality of care given. Although the data was collected from a district hospital, the hospital is also involved in research and may not be quite typical of a district hospital in developing country setting. It has better laboratory services and with paediatrician involved in care. This may mean that treatment could be changed based on the laboratory finding or expert opinion. However, in as much as ethically possible, care was strictly according to the WHO guidelines in terms of available medication. Lastly, the data was obtained from one centre and this may limit the generalizability of the scores to other countries or settings.

IMPLICATION

By using simple clinical signs and symptoms, the scores that are able to identify most of the children with SAM at risk of dying have been developed. However, the poor specificity means that a lot of children with SAM are included and does not relieve the burden in hospitals. Although oedema was found to be prognostic, nearly 40% of children admitted had oedema but there was no evidence for interaction with other prognostic indicators. Further classification of the severity of oedema, may help improve on the specificity. Despite this the identified prognostic signs point to likely complications that are amenable to interventions. Electrolyte imbalances are as a result of dehydration, dehydration remains a controversial are in management of SAM. Clinical trials of different fluid interventions, where children are stratified according to the scores may resolve this problem. It was interesting to note that a third of the patients scored zero and mortality was less than 5 %. This may indicate that the current WHO guidelines on the management of SAM may not be adequately addressing complication in the remaining two thirds of children.

CONCLUSION

Simple signs and symptoms have been used to develop prognostic scores for SAM. Despite having poor specificity, they all had good sensitivity to identify most of those at high risk. The scores did not perform any better than a previously developed score, despite having different

prognostic variables. If these scores are validated in other settings, they can be used to stratify patients in intervention studies. The prognostic indicators identified were features of dehydration or shock. These are two key areas that have been identified previously and studies on the adequacy of the current guidelines on this area are required.

REFERENCES

1. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet*. 2003 Jun 28;361(9376):2226-34.
2. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008 Jan 19;371(9608):243-60.
3. Collins S, Dent N, Binns P, Bahwere P, Sadler K, Hallam A. Management of severe acute malnutrition in children. *Lancet*. 2006 Dec 2;368(9551):1992-2000.
4. Manary MJ, Hart CA, Whyte MP. Severe hypophosphatemia in children with kwashiorkor is associated with increased mortality. *J Pediatr*. 1998 Dec;133(6):789-91.
5. Schofield C, Ashworth A. Why have mortality rates for severe malnutrition remained so high? *Bull World Health Organ*. 1996;74(2):223-9.
6. WHO. Management of severe malnutrition: a manual for physicians and other senior health workers. *Journal [serial on the Internet]*. 1999 Date: Available from: <http://whqlibdoc.who.int/hq/1999/a57361.pdf>.
7. Babirekere-Iriso E, Musoke P, Kekitiinwa A. Bacteraemia in severely malnourished children in an HIV-endemic setting. *Ann Trop Paediatr*. 2006 Dec;26(4):319-28.
8. Noorani N, Macharia WM, Oyatsi D, Revathi G. Bacterial isolates in severely malnourished children at Kenyatta National Hospital, Nairobi. *East Afr Med J*. 2005 Jul;82(7):343-8.
9. Reed RP, Wegerhoff FO, Rothberg AD. Bacteraemia in malnourished rural African children. *Ann Trop Paediatr*. 1996 Mar;16(1):61-8.
10. Nolan T, Angos P, Cunha AJ, Muhe L, Qazi S, Simoes EA, et al. Quality of hospital care for seriously ill children in less-developed countries. *Lancet*. 2001 Jan 13;357(9250):106-10.
11. Molyneux E, Ahmad S, Robertson A. Improved triage and emergency care for children reduces inpatient mortality in a resource-constrained setting. *Bull World Health Organ*. 2006 Apr;84(4):314-9.

12. Maitland K, Berkley JA, Shebbe M, Peshu N, English M, Newton CR. Children with severe malnutrition: can those at highest risk of death be identified with the WHO protocol? *PLoS Med.* 2006 Dec;3(12):e500.
13. Heikens GT, Bunn J, Amadi B, Manary M, Chhagan M, Berkley JA, et al. Case management of HIV-infected severely malnourished children: challenges in the area of highest prevalence. *Lancet.* 2008 Apr 12;371(9620):1305-7.
14. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. *Crit Care Med.* 1996 May;24(5):743-52.
15. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med.* 2003 Feb;29(2):278-85.
16. Graciano AL, Balko JA, Rahn DS, Ahmad N, Giroir BP. The Pediatric Multiple Organ Dysfunction Score (P-MODS): development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children. *Crit Care Med.* 2005 Jul;33(7):1484-91.
17. Bitwe R, Dramaix M, Hennart P. [Simplified prognostic model of overall intrahospital mortality of children in central Africa]. *Trop Med Int Health.* 2006 Jan;11(1):73-80.
18. Dramaix M, Brasseur D, Donnen P, Bawhere P, Porignon D, Tonglet R, et al. Prognostic indices for mortality of hospitalized children in central Africa. *Am J Epidemiol.* 1996 Jun 15;143(12):1235-43.
19. Dramaix M, Hennart P, Brasseur D, Bahwere P, Mudjene O, Tonglet R, et al. Serum albumin concentration, arm circumference, and oedema and subsequent risk of dying in children in central Africa. *BMJ.* 1993 Sep 18;307(6906):710-3.
20. Savadogo L, Zoetaba I, Donnen P, Hennart P, Sondo BK, Dramaix M. [Management of severe acute malnutrition in an urban nutritional rehabilitation center in Burkina Faso]. *Rev Epidemiol Sante Publique.* 2007 Aug;55(4):265-74.
21. Erinoso HO, Akinbami FO, Akinyinka OO. Prognostic factors in severely malnourished hospitalized Nigerian children. Anthropometric and biochemical factors. *Trop Geogr Med.* 1993;45(6):290-3.
22. Gernaat HB, Dechering WH, Voorhoeve HW. Mortality in severe protein-energy malnutrition at Nchelenge, Zambia. *J Trop Pediatr.* 1998 Aug;44(4):211-7.

23. Sunguya BF, Koola JI, Atkinson S. Infections associated with severe malnutrition among hospitalised children in East Africa. *Tanzan Health Res Bull.* 2006 Sep;8(3):189-92.
24. Ogbeide O, Osuhor PC. Morbidity and mortality patterns among malnourished children in Benin City, Nigeria. *Trop Doct.* 1984 Oct;14(4):178-80.
25. Bahwere P, De Mol P, Donnen P, Dramaix-Wilmet M, Butzler JP, Hennart P, et al. Improvements in nutritional management as a determinant of reduced mortality from community-acquired lower respiratory tract infection in hospitalized children from rural central Africa. *Pediatr Infect Dis J.* 2004 Aug;23(8):739-47.
26. Prudhon C, Golden MH, Briend A, Mary JY. A model to standardise mortality of severely malnourished children using nutritional status on admission to therapeutic feeding centres. *Eur J Clin Nutr.* 1997 Nov;51(11):771-7.
27. Central Bureau of Statistics Kenya. Geographic Dimensions of Well-Being in Kenya: Who and Where Are the Poor? A Constituency Level Profile. Journal [serial on the Internet]. Date: Available from: <http://www.knbs.or.ke/surveys/poverty/pdf/KenyaPovAtlasIIfinal2cl.pdf>.
28. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996 Feb 28;15(4):361-87.
29. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol.* 2006 Oct;59(10):1087-91.
30. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med.* 2006 Jan 15;25(1):127-41.
31. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ.* 2009;338:b605.
32. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. *BMJ.* 2009;338:b604.
33. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology.* 1982 Apr;143(1):29-36.
34. Soreide K. Receiver-operating characteristic curve analysis in diagnostic, prognostic and predictive biomarker research. *J Clin Pathol.* 2009 Jan;62(1):1-5.

35. Chen LC, Chowdhury A, Huffman SL. Anthropometric assessment of energy-protein malnutrition and subsequent risk of mortality among preschool aged children. *Am J Clin Nutr.* 1980 Aug;33(8):1836-45.
36. Ronsmans C, Chowdhury ME, Dasgupta SK, Ahmed A, Koblinsky M. Effect of parent's death on child survival in rural Bangladesh: a cohort study. *Lancet.* 2010 Jun 5;375(9730):2024-31.
37. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. . *Lancet.* 2000 Feb 5;355(9202):451-5.

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I am appreciative of the fieldworkers, the clinical and nursing staff of paediatric ward and all of the other staff at Kilifi District Hospital and KEMRI who assisted in patient care and data collection for this study. I owe the greatest vote of thanks to the mothers, fathers and children who participated in the study.

Finally, I am especially grateful to my wife, my son and my daughter for their patience, understanding and moral support for the entire period I was away from home.

APPENDIX

APPENDIX 1: A LIST OF ALL CLINICAL, DEMOGRAPHIC AND LABORATORY VARIABLES COLLECTED FROM EACH PATIENT ON ADMISSION AND DISCHARGE.

Variable Name	Description	Variable Name	Description
serial	unique kemri-kdh admn #	percussion_dull	
person	unique DSS person ID	percussion_a	
hosp_ip	kdh in-patient govt #	percussion_p	
names	person names	crackles	
sex	male/female 1/0	crackles_a	
date_birth	date of birth ddmmyyyy	crackles_p	
date_admission	date admitted kdh ddmmyyyy	wheeze	
time_admission	time admitted 24hr	head_nodding	
status	admission process status	unable_to_drink	
weight	admission weight kg	candida_oral	
length	admission length cm	jaundice	
length_type	lying or standing	liver_size	
muac	mid upper arm circum cm	spleen_size	
head_circ	head circumference cm	oedema	
born_in_hosp		wasting	visible severe wasting
fever	history of fever	skin_hair	
fever_drn	duration of fever days	desquamation	
cough	history of cough	conscious_level 6	
cough_drn	cough duration days	unconscious_drn int	
breathing_diff	history breathing diff	smac_conscious 1	
diarrhoea	history of diarrhoea	agitation	
diarrhoea_drn	diarrhoea duration days	neck_stiffness	
diarrhoea_blood	blood in diarrhoea	fontanelle_bul	
vomiting	history of vomiting	fit_current	

vomiting_drn	vomiting duration days	bcs_verbal	
convulsion	history of convulsions	bcs_motor	
convulsion_tot		bcs_eyes	
conv_24hr		all_other_exam	
convulsion_prev		problem_list	0 admission diagnosis
conv_type		bcs	blantyre coma score
perinatal_cry		ht_for_age	height for age z score
perinatal_bf		wt_for_age	weight for age z score
premature		wt_for_ht	weight for height z score
low_birth_wt		date_adm_kemri	date admit kemri ward ddmmyyyy
perinatal_jaun	Perinatal jaundice	date_disch	date discharged ddmmyyyy
perinatal_prob	Perinatal problems	time_disch	time discharged 24hr
perinatal_admn	Admitted perinatally	disch_type	how discharged
unaided_dev	Current development stage	transfused	
mum_dead	Mum dead	weight_disch	discharge weight kg
dad_dead	Dad dead	diag1_disch	primary discharge diagnosis
free_text		diag2_disch	secondary discharge diagnosis
bcg_scar		comment	
heart_rate	heart beats per minute	hb	haemaglobin
resp_rate	breaths per minute	hct	haematocrit
oxysat	%O2 saturation by oxymetry	mcv	mean cell volume
temp_axill	axillary temperature OC	platelets	
temp_gradient	temperature gradient	mps100wbc	malaria

			parasites/100 wbc
pulse_vol	pulse volume	mps500rbc	malaria parasites/500 rbc
cap_refill	capillary refill sec	wbc	white blood cell count
pallor		rbc	red blood cell count
cyanosis		species	plasmodium species
clubbing		ph	Blood gas PH
lymphadenopathy		pco2	Blood gas Pco2
sunken_eye	Presence of sunken eyes	bases	base excess
dec_skin_turgor	decreased skin turgor	potassium	Serum potassium
skin_infection	Skin infection	sodium	Serum sodium
ears_discharge	Ear discharge	creat	creatinine
flaring	Nasal flaring	bilirubin	
indrawing	Lower chest indrawing	bloodglu	blood glucose
resp_deep	respiration deep	organism	blood culture isolate
resp_irregular	Irregular respiration	csfglu	Sugar in csf
stridor		hiv_status	hiv_results

APPENDIX 2: LOCAL ETHICAL APPROVAL



KENYA MEDICAL RESEARCH INSTITUTE

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KEMRI/RES/7/3/1

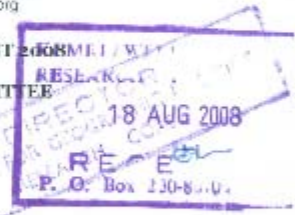
05 AUGUST 2008

FROM: SECRETARY, KEMRI/NATIONAL ETHICAL REVIEW COMMITTEE

THRO: DR. N Peshu,
THE DIRECTOR, CGMR-C,
KILIFI

TO: Kathryn Maitland (PRINCIPAL INVESTIGATOR)

RE: SSC PROTOCOL No. 927: A prospective study of severe protein caloric malnutrition in hospitalized Kenyan children



Dear Madame,

Reference is made to your letter dated May 21 2008.

The above study was given the initial approved on June 8, 2005 at which time you expected the lifespan of the study to be 3 years, therefore the study would have ended mid 2008. Two years later in May 27, 2007 you requested for an extension of the study for a further period of 3.5 years in which time you intended to initiate an intervention and physiological study that would enable you to follow up and monitor the children.

This request was accompanied by several amendments which included:

1. Change of Principal Investigator from Sarah Atkinson to Kathryn Maitland
2. The addition of direct testing and counseling (DCT) for HIV status to reflect national and local policy, which lead to a subsequent change in the Informed Consent Document (ICD)
3. A clinical evaluation once children stabilized at one (1) week, to tailor further management for children presenting with chronic childhood conditions

The above request however was received by this Committee in April this year which gave rise to our letter dated April 17, 2008 asking for the status of the protocol, to which you responded on April 24, 2008.

The letter of 24th April 2008 includes in the final paragraph your planned studies which include:

1. Pharmacokinetics of ciprofloxacin in malnourished children
2. Audit of care pathways for investigation and treatment of diarrhea in malnutrition
3. measuring outcome for HIV positive patients with malnutrition in the light of increasing use of cotrimoxazole prophylaxis and an antiretroviral treatment

Presumably the permission to continue to recruit new patients will be for the planned activities which will further extend the study until 2012. This request is granted approval and the provisional approval granted by the Chairman of the KEMRI/NERC for continuation of the study until April 2009 is also ratified. You may continue with your study and we look forward to your annual progress report in due time.

Sincerely,

Ruth Kithinji
R.C. KITHINJI,
FOR: SECRETARY,
KEMRI/NATIONAL ETHICAL REVIEW COMMITTEE

In Search of Better Health



APPENDIX 3: Combined Academic, Risk assessment and Ethics (CARE) approval form FOR MSc PROJECT REPORTS

London School of Hygiene & Tropical Medicine

(University of London)



**COMBINED ACADEMIC, RISK ASSESSMENT AND ETHICS (CARE)
APPROVAL FORM for MSc Project Reports**

This form must be completed electronically. For detailed guidance, please refer to the **Project Handbook for your course.*

SECTION 1 – STUDENT AND COURSE INFORMATION

MSc DETAILS AND DEADLINES (deadlines to be communicated by Course Director)

Academic Year	2009-10
MSc course (and stream, where applicable)	EPIDEMIOLOGY
Deadline for Supervisor approval	Friday 19th Feb 2010
Deadline for Course Director approval	
Deadline for submission to Ethics Committee	Friday 26 March 2010
Target for approved form to be passed to TSO	Friday 30 April 2010

STUDENT, SUPERVISOR AND TUTOR DETAILS (to be completed by student)

Full name of student	
Student email address	
Year of study (part-time students only)	<input checked="" type="checkbox"/> First Year <input type="checkbox"/> Second Year
Supervisor name	
Supervisor email address	
Supervisor status (at time of this version of the form being completed)	<input type="checkbox"/> Confirmed <input checked="" type="checkbox"/> Provisional <input type="checkbox"/> Still to be identified
Name of personal tutor (where Supervisor is still to be identified)	

SECTION 2 – APPROVAL AND SUBMISSION STATUS

**Students please note: It is a requirement of your LSHTM degree that you obtain all required approvals before beginning your project work. To comply with legal requirements, your Supervisor and Course Director must specifically give Risk Assessment approval. Ethical approval must also be obtained if required (answers in Section 5 will help determine if so).*

STUDENT DECLARATION (to be completed for all projects)

I agree to conduct my project on the basis set out in this form, and to consult staff (initially, my Supervisor) if making any subsequent changes – especially

any that would affect the information given with respect to ethics approval.		
I agree to comply with the relevant safety requirements, and will submit a separate request for LSHTM travel insurance where relevant.		<input checked="" type="checkbox"/>
<i>*Where seeking ethical approval for a study involving human subjects, please also attach copies of any information sheets, consent forms, and other relevant documents.</i>		
Date of declaration	12/02/2010	

**Further note: when submitting your final project report at the end of the summer, you should also include a copy of your approved CARE form (which will be seen by the project markers); but to preserve anonymity, the page above – with your name – should be omitted.*

STAFF APPROVAL

**Staff please note: Sections 3 and 4 of the form should be completed by the student before you are asked to sign. If you tick 'no' to any of the 'Yes/No' questions below, or disagree with any of the statements given, or have any other concerns, then you should not give approval – instead, please contact the student immediately to inform them of your concerns and discuss changes which they may need to make before you may be willing to give approval.*

**Supervisors and Course Directors should also be aware that in the exceptional case of a request to undertake a project in a country or region to which the Foreign & Commonwealth Office advise against travel, the student would need to fill out a separate form which will then need further School-level approval by the Safety Manager and Secretary & Registrar.*

SUPERVISOR'S APPROVAL (required for all projects – this approval should be given first)

I agree that Section 3 of this form is a reasonable summary of the proposed project.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
I agree that responses in Section 4 of this form address the main risks connected with a project of this nature.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Name of Supervisor (if not yet identified, personal tutor <u>or</u> Course Director should approve)	
Date of approval	16/2/2010

COURSE DIRECTOR'S APPROVAL (required for all projects – should follow Supervisor approval)

I agree that the academic content of the proposed project, set out at Section 3 of this form, is suitable for this MSc.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
I agree that responses in Section 4 of this form address the main risks connected with a project of this nature.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Name of Course Director (or nominee)	Punam Mangtani and Sara Thomas
Date of approval	17/03/2010

DEPARTMENTAL SAFETY SUPERVISOR'S APPROVAL (only required if project involves working with pathogenic organisms, human blood or radiochemicals – should follow Supervisor approval)

I agree that the proposed project, as set out in this form and particularly Section 4, may proceed.	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

Name of Departmental Safety Supervisor (or nominee)	
Date of approval	

ETHICAL APPROVAL (required for all projects involving human subjects or human data, except for public domain data that cannot enable the identification of living people – NB that Supervisor approval **must** have been received before the application is submitted to the Ethics Committee)

Date application received	24/03/2010
Ethics Committee application number assigned	009/147
On behalf of the Ethics Committee, I approve the project proposal set out on this form.	x <input type="checkbox"/> Yes <input type="checkbox"/> No
Name of Ethics Committee scrutineer	Paula Elliott
Date of approval	08/04/2010

SECTION 3 – APPLICATION FOR ACADEMIC APPROVAL

**All students should complete all sub-sections (3.1, 3.2 and 3.3); if particular questions are not applicable to you then please write 'N/A'.*

3.1 PROJECT OUTLINE (should not normally exceed 750 words total)

Proposed project title: (should not normally exceed 20 words)

DEVELOPMENT AND VALIDATION OF A RISK SCORE FOR PREDICTING DEATH IN CHILDREN WITH SEVERE ACUTE MALNUTRITION

Proposed project type:

**See course-specific section of Project Handbook for details of project types permitted for each MSc. Be aware that restrictions may apply for individual courses.*

DATA ANALYSIS

Proposed project length:

**For almost all students, this will be 'Standard'. Long and extended projects are only available for certain ITD courses; they have a different schedule and allow a slightly greater word count.*

Standard Long Extended

Background: (about 200 words)

**Indicate why this topic is of interest or relevance.*

**If the project involves work with a specific organisation please give details.*

**Please give any other details specifically relevant for consideration by the Ethics Committee, e.g. related to purpose.*

The current mortality rate in children with severe acute malnutrition (SAM) in sub Saharan Africa is high despite close adherence to WHO guidelines for nutritional management¹. It has been suggested that the WHO danger signs are not sensitive enough to identify all children at high risk of dying². There are limited studies that have identified high risk children. Some studies have identified electrolyte imbalance, hypoalbuminaemia, oedema and severity of wasting as risk factors³⁻⁵. Maitland et al

proposed a triage system of SAM to high, medium and low risk². However, there was no internal or external validation. Recent advances have seen children with severe malnutrition, who do not have any medical complications, managed successfully in outpatient therapeutic centres, but, there remains no clear way of identifying which children with SAM require hospital management.

Prognostic scores have been used for a long time especially among high mortality groups like cancer patients, burns patient and patients in intensive care units. Identifying children with severe malnutrition who are likely to die will help in appropriate resource allocation and tailoring therapy to match the risk and facilitate planning of clinical trials. Kilifi Severe malnutrition Programme (KISMAP) has been collecting data on all children admitted in Kilifi District hospital (KDH) with SAM since 2005. There is no Outpatient therapeutic center hence all SAM cases identified in the community and referred to hospital are seen in the program.

Hypothesis: (about 30 words, where applicable)

NONE

Overall aim of project: (about 30 words)

To develop and validate practical prognostic models for death in children admitted to hospital with SAM

Specific objectives of project: (about 70 words)

- To develop and validate practical prognostic models for death in hospital and death within 7 days of admission in children with SAM.
- To describe the variation in predictive value of the model among children with HIV or underlying chronic conditions(sickle cell disease, cerebral palsy, heart disease).
- To describe variation in the model with and without admission laboratory results.

Proposed methods: (about 200 words)

Please summarise methods, and include **any relevant details for consideration by the Ethics Committee such as numbers of participants and procedures to be performed.*

Primary endpoint

- Death before discharge

Secondary

- Mortality within 7 days of admission

Study population:

All children aged > 6 months admitted to KDH with features of severe malnutrition, who consented to the descriptive study.

Sample size

The dataset contains more than 1000 participants with case fatality rate of approximately 20%. As

shown in the table below, the data provides adequate power to identify a threefold and two fold increase in odds if the exposure prevalence is >1% and >5% respectively. The Type I error associated with this test is 0.05.

Exposure Prevalence	Odds Ratio			
	1.5	2.0	3.0	5.0
1	.12	.26	.54	.87
3	.20	.49	.88	.99
5	.28	.65	.97	1
8	.37	.80	.99	
10	.42	.86	.99	
15	.53	.94		
20	.60	.97		
25	.68	.98		
30	.69	.99		
40	.73	.99		
50	.72			

Procedures

Data collected from children admitted to KDH with SAM between June 2005 and June 2009 and who consented to the descriptive study of SAM will be used. The data from clinical and laboratory databases will be transferred into STATA, merged, and cleaned. It will be checked and cases with missing observations dropped or imputed from the available data. Continuous variables will be converted into categorical variables using sensible clinical cut offs or percentiles.

The dataset will be split into a derivative and validation data. Using the derivative dataset, associations between potential predictor variables and death will be described using appropriate tests (unpaired *t* test, Chi square test, Fisher exact test).

Variables to be used in model building will be selected based on the p value or odds ratio or if previously identified as predictors of death. Variables identified in the multi-variable model will be assigned weights and a risk score calculated for each patient. The predictive accuracy of the prognostic score will be examined in the validation dataset using ROC/C statistic

References: (max 150 words)

**List any key references which will shape the project, including for methods to be used. It*

should not normally be necessary to quote more than 5 references.

1. Ashworth, A., et al., *WHO guidelines for management of severe malnutrition in rural South African hospitals: effect on case fatality and the influence of operational factors*. Lancet, 2004. **363**(9415): p. 1110-5.
2. Maitland, K., et al., *Children with severe malnutrition: can those at highest risk of death be identified with the WHO protocol?* PLoS Med, 2006. **3**(12): p. e500.
3. Erinoso, H.O., F.O. Akinbami, and O.O. Akinyinka, *Prognostic factors in severely malnourished hospitalized Nigerian children. Anthropometric and biochemical factors*. Trop Geogr Med, 1993. **45**(6): p. 290-3.
4. Dramaix, M., et al., *Prognostic indices for mortality of hospitalized children in central Africa*. Am J Epidemiol, 1996. **143**(12): p. 1235-43.
5. Tolboom, J.J., et al., *Severe protein energy malnutrition in Lesotho, death and survival in hospital, clinical findings*. Trop Geogr Med, 1986. **38**(4): p. 351-8.

Prior work: (only where relevant; max 100 words)

**Indicate any previous work you have done related to this project topic, including student work, professional work, or publications.*

I have been working as a medical officer within the KISMAP. My main duties involved patient recruitment and care and supervising data collection. I have published a paper on the prognostic value of urine dipstick in SAM.

3.2 FEASIBILITY (about 100 words total – but can write more or write less if appropriate)

What could cause this project to fail, i.e. prevent you from achieving your objectives?

**Please indicate any aspects of your proposed approach which could potentially experience difficulties, e.g. delays with permissions, data collection or storage problems, lack of sufficient comparable information, etc. You may also wish to mention any wider matters which could affect your project, e.g. civil unrest, natural disasters, transport availability.*

Problems

- Some missing data
- Limited power

What alternative plans do you have in case you encounter any of the potential problems you have identified?

Alternative

- Analyse the 2001-2004 dataset using discriminate analysis and include a validation dataset. This data has been previously analyzed and published using logistic regression but no validation was done for the model developed.
- Design a study protocol

3.3 INTELLECTUAL PROPERTY, COPYRIGHT AND OTHER PERMISSIONS

**Please also see Section 5.2 regarding any specific data rights limitations arising from local*

ethical or research governance requirements

If you expect to use existing data, how will you obtain it and what permissions will be required?

WRITTEN PERMISSION HAS ALREADY BEEN OBTAINED FROM THE PRINCIPAL INVESTIGATOR

Having considered whether intellectual property rights (IPR) or copyright issues may affect your project, will any specific agreements be required?

**Please tick all boxes that apply, and attach copies of any forms/agreements (even if in draft).*

- No specific IPR, Copyright or permissions issues should apply to this project (student retains Copyright and related IPR by default, in line with LSHTM registration declaration)
- IPR to be retained by LSHTM (specific LSHTM form to be completed)
- Copyright to be transferred to LSHTM (specific LSHTM form to be completed)
- IPR, Copyright or other agreements/permissions required with external parties/organisations

Please give any further relevant details about IPR, copyright or other permissions.

SECTION 4 – APPLICATION FOR RISK ASSESSMENT APPROVAL

**All students should answer all questions in sub-section 4.1; this will make clear which of the following sub-sections you need to complete.*

Ensuring safety during project work is the responsibility of each individual student, and not of LSHTM or LSHTM staff. **Please see the Project Handbook for further guidance.*

4.1 TYPE OF RISK (to be completed by all students)

Where will the project be carried out? (please tick all that apply)

**Note that work away from LSHTM or outside the UK means any form of work for your project, not just primary data collection. Some courses may have specific restrictions on this.*

- All work will take place either at LSHTM, in libraries in the UK, or at my personal residence in the UK.** [If so, you do not need to complete either section 4.2 or section 4.3]
- Some work will take place in the UK that is away from LSHTM sites in London, is non-Library-based, and is not at my personal residence.** [If so, section 4.2 on 'Work away from LSHTM' must be completed]
- Some work will take place at my personal residence outside the UK** [If so, section 4.3 on 'Work outside the UK' must be completed]
- Some work will take place outside the UK that is not at my personal residence** [If so, both sections 4.2 and 4.3 on 'Work away from LSHTM' and 'Work outside the UK' must be completed]

Will the project involve working with or handling any of the following materials?

- Pathogenic organisms** Yes No
- Human blood** Yes No
- Radiochemicals** Yes No

[If 'Yes' to any of the above, Sections 4.4 and 4.5 must be completed]

Are any other potentially hazardous activities likely to be carried out during the project?

Yes No

[If 'Yes', Section 4.5 must be completed]

Do any special requirements (e.g. disability-related issues) or other concerns need to be taken into account for either you as a student, study participants or colleagues?

Yes No

[If 'Yes', Section 4.6 must be completed]

4.2 WORK AWAY FROM LSHTM (to be completed if any work will be done away from LSHTM, other than at your home or at libraries elsewhere in the UK)

Will the project be based in an established hospital, college, research institute, NGO headquarters, field station or other institutional site? If 'Yes', please give the name and location of the site(s); describe approximately what proportions of your project will be spent there; and state name and role of person who has confirmed willingness to support you at each site (indicating extent of correspondence, especially what they have confirmed in writing).

Yes No

Will you have an 'external supervisor', co-supervisor or other main advisor, or be working with any specific organisation(s), during your work away from LSHTM? If 'Yes', please indicate the name, role, contact details, and level of support that any such external advisors are expected to provide, and give details about any organisations you will be working with.

Yes No

Will the project involve personal visits, interviews or interactions with people in their homes, workplaces, community settings or similar? If 'Yes', please give details, including approximately what proportion of your project this will involve.

Yes No

Will the project involve lone/isolated work or significant travel? If 'Yes', please give details, including approximately what proportion of your project this will involve, and state how you can be contacted while working or travelling.

Yes No

What arrangements are proposed for contact with your main supervisor while you are away from LSHTM? Indicate expected ease and frequency of contact, and communication methods to be used.

Please tick to confirm:

I have read the LSHTM Code of Practice on off-site work.

4.3 WORK OUTSIDE THE UK (to be completed if any work will be done outside the UK)

What form of project work will be undertaken outside the UK? (please tick all that apply)

Work at my family home or personal residence only

Work at an established hospital, college, research institute, NGO headquarters, field station or other institutional site

Work away from my personal residence or an established site

**Note that for either the second or third options, you should also have completed Section 4.2.*

Name the country/countries and region(s) in which work will be undertaken:

Country or countries:

Region(s) :

Do the Foreign & Commonwealth Office's (FCO) Travel Advice Notices (www.fco.gov.uk/en/travelling-and-living-overseas/travel-advice-by-country/) advise against travel to the regions(s), country or countries involved?

Yes No

Note that if 'Yes', the School will not normally permit such travel for project work. In **exceptional circumstances only, requests may be considered by the Safety Committee and require approval by the Safety Manager and Secretary & Registrar.*

Please tick to confirm:

I understand that LSHTM travel insurance is required for any international travel as part of my project.

**Travel insurance can be applied for using a separate form.*

4.4 WORK WITH HAZARDOUS SUBSTANCES (to be completed if the project involves any work with pathogenic organisms, human blood or radiochemicals – NB that this will require approval by the Departmental Safety Supervisor)

Name the organism or organisms to be used:

Identify all potential routes of infection:

Name the radiochemical or radiochemicals to be used:

List laboratories where work with pathogens or radioisotopes will be carried out:

List disinfectants to be used, and describe arrangements for disposal of used material:

Will or might Health Surveillance be required for you or any staff working with you? If 'Yes', please give details.

Yes No

4.5 PRECAUTIONS AGAINST HAZARDS (to be completed if any potentially hazardous activities are likely to be carried out during the project. Refer to Project Handbook and School safety documentation for further information. Departmental Safety Supervisor's approval should be obtained where felt appropriate by project Supervisor.)

Indicate any procedures, activities or aspects of the proposed project which may entail hazards (including work with hazardous substances as per Section 4.4, or anything else relevant). Please set distinct hazards out separately, in a numbered list.

Indicate the precautions you will take to prevent or mitigate such potential hazards.
Please number these to refer to the specific hazards identified in the preceding question.

4.6 SPECIAL REQUIREMENTS (to be completed if the project involves any special requirements, e.g. disability-related issues, or other concerns that need to be taken into account for either you as a student, study participants or colleagues)

What special requirements or concerns need to be taken into account?

Do these need to be considered in planning arrangements?

Yes No

If 'Yes', please give details.

Do these impact on supervision arrangements?

Yes No

If 'Yes', please give details.

Does the project location need to be considered in relation to these?

Yes No

If 'Yes', please give details.

Do arrangements for access to specialist medical treatment need to be considered?

Yes No

If 'Yes', please give details.

SECTION 5 – APPLICATION FOR ETHICS APPROVAL

**All students should answer all questions in sub-sections 5.1 and 5.2. Answers to 5.1 will make clear whether approval by the LSHTM Ethics Committee is necessary, and which later sub-sections you may need to complete. Section 5.2 covers any external approvals required.*

5.1 SCOPE OF STUDY (to be completed by all students)

Before completing this part of the form, please read the Ethics Approval Policy & Procedure plus guidance notes at <http://intra.lshtm.ac.uk/reference/ethicsstuds.html> . This describes what to do next if formal LSHTM ethics approval is required. NB that supervisor approval must be obtained **before an application is submitted to the Ethics Committee.*

Which of the following applies to your project? (please tick one option only)

**Note – the term 'human data' includes any documentary data, datasets or biological samples.*

Project does not involve any human subjects or any human data. [If so, formal LSHTM ethics approval is not required and you do not need to complete Sections 5.3 or 5.4]

Project involves human data, but all this human data is fully in the public domain.

[If so, formal LSHTM ethics approval is not required and you do not need to complete Sections 5.3 or 5.4]

**Public domain human data must be: available to any member of the public without special permission; to which access is not restricted in any way; and which does not enable the identification of living people, either directly or by linking to other data.*

Project involves some non-public-domain human data, all of which was previously collected in another study or studies. [If so, formal LSHTM ethics approval is required and Section 5.3 must be completed]

Project involves some additional collection of data, further to an ongoing or previously completed study or studies. [If so, formal LSHTM ethics approval is required and Section 5.4 must be completed]

Project is a completely new study which will involve human subjects or human data. [If so, formal LSHTM ethics approval is required and Section 5.4 must be completed]

5.2 LOCAL ETHICAL APPROVAL OR RESEARCH GOVERNANCE APPROVAL (to be completed by all students)

** As well as approval from the LSHTM Ethics Committee, projects may require specific approval from other involved or responsible bodies. For example, in the UK you may need specific authorisation to work in an NHS facility, or to work with vulnerable groups such as patients or children. Outside the UK a wide range of requirements may apply e.g. from local or national Ethics Committees, government departments etc. **Students must investigate all potential local approval required for your project work. Failure to check or gain any necessary external approval may invalidate LSHTM approval.***

Is local approval required for the work being done (whether this approval is still to be obtained, or has already been granted)?

Yes No

**This should include any forms of ethical approval, research governance approval or other specific permissions that may apply.*

If 'Yes', give details of local approval to be obtained (this must be in place before commencing fieldwork) or which has already been granted.

**Please name all bodies whose approval is required, or indicate where work is expected to take place using permissions already granted for a 'parent' project. Where approval has already been granted, quote approval reference numbers and if possible give web links to documents.*

If 'No', explain why formal local approval is not required, and describe any less formal permissions, invitations or support you are being given for this work.

**If you will be working away from LSHTM with human subjects or human data, but cannot identify a local Ethics Committee or believe that no formal approval is required, then please give details and explain what you have done to check this. In such cases, if you do not have formal approval you should always demonstrate appropriate local support, such as correspondence with local government officials or an involved Non-Governmental Organisation.*

THE STUDY PROTOCOL FROM WHICH THE DATASET WAS OBTAINED, WAS APPROVED BY THE KENYA MEDICAL RESEARCH INSTITUTE SCIENTIFIC STEERING COMMITTEE AND THE NATIONAL ETHICS REVIEW COMMITTEE. THE APPROVAL LETTERS ARE ATTACHED.

For data to be used or collected in the project, will any specific data rights permissions be required or usage limitations apply?

Yes No

5.3 PROJECTS USING ONLY PREVIOUSLY-COLLECTED HUMAN DATA (to be completed if project involves non-public-domain human data, datasets or biological samples previously collected in another study or studies; if collecting any new data, complete Section 5.4 instead)
**Further guidance is given at <http://intra.lshtm.ac.uk/reference/ethicsstuds.html>*

Summary of purpose and methods of the original study or studies: (max 100 words)

The aim of the study is to provide a comprehensive description of the clinical and laboratory features of severe malnutrition in a hospital cohort of Kenyan children and prospectively identify life-threatening features and complications, which may be amenable to treatment interventions, and thus improve current management guidelines.

It is a prospective observational study, involving children >6 months old admitted to KDH with protein-calorie malnutrition. Data on clinical and biochemical parameters in these children is collected on admission and daily until discharge or death.

Give details of all approvals under which the original study or studies took place:

**Please quote names of Ethics Committees and approval reference numbers (required if previous approval was from LSHTM); if possible give web link to original study application.*

Ethical approval was obtained from the KEMRI/National Ethical Review Committee(SSC protocol No 927). Copies of the approval are attached.

Proposed study: Ensure that the project outline given in Section 3.1 states the purpose, methods and procedures of the new work to be done in your project, and describes how this builds on the previous study or studies (for which participants will already have been recruited, data or samples collected, and procedures performed). Do not reproduce here.

<p>Will your analyses be for purposes <u>not covered</u> by the original application detailed above? If 'Yes', indicate how you will obtain (i) permission to use the data from the principal investigator responsible for each original study; and (ii) retrospective consent, where appropriate, from the participants in each original study.</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
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<p>Does the project involve analysis of documentary information and/or data already collected from or about human subjects? If 'Yes', specify analyses briefly.</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
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Univariate analysis of association between symptoms and signs and laboratory data with death will be done to identify risk factors. Using logistic regression, this will be fit into a model. We will use the variables in the final model to develop a prediction score by applying a weighting for each variable. The score developed will then be validated.

<p>Does the project involve laboratory analysis of human biological samples already collected, or new or additional analysis of stored samples? If 'Yes', specify the laboratory analyses or tests to be performed.</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
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Specify how confidentiality will be maintained. When small numbers are involved, indicate how possible identification of individuals will be avoided.

Participants are identified by serial number and no personal identifiers are kept.

5.4 PROJECTS COLLECTING ANY NEW HUMAN DATA (to be completed if project involves collection of human data, datasets or human biological samples – either as a completely new study, or collecting additional data further to an ongoing or previously completed study)

**Further guidance is given at <http://intra.lshtm.ac.uk/reference/ethicsstuds.html>*

Proposed study: Ensure that the project outline given in Section 3.1 contains sufficient detail (inc. purpose, methods, procedures for both new data collection and any work building on previous studies), so as to allow the Ethics Committee to make an informed decision without reference to other documents. Do not reproduce here.

Is your project a randomised trial? Yes No

Will any human biological samples be collected? If 'Yes', specify details. Yes No

Will any human biological material be stored at LSHTM for more than 24 hours? If 'Yes', specify which samples and how they will be stored. Yes No

**Further guidance is given at <http://intra.lshtm.ac.uk/safety/Safety%20manual-3-HTA.pdf>*

Specify the number - with scientific justification for sample size – age, gender, source and method of recruiting subjects for the study.

State the location and likely duration of new or additional human data collection, and the extent to which this will be carried out by you alone, or in collaboration with others, or by others.

State the potential distress, discomfort or hazards, and their likelihood, to which research subjects may be exposed (these may include physical, biological and/or psychological hazards). What precautions are being taken to control and modify these hazards?

Specify how confidentiality will be maintained. When small numbers are involved, indicate how possible identification of individuals will be avoided.

State the manner in which consent will be obtained from subjects and supply copies of the information sheet and consent form.

- Written consent is normally required. Where not possible, explain why and confirm that a record of those giving verbal consent will be kept.
- Where appropriate, please state if and how the information and consent form will be translated into local language(s).

As well as collecting new data, will your project also make use of any human data or biological samples collected in a previous study or studies? If 'Yes', summarise the purpose and methods of the original study or Yes No

studies – for which participants will already have been recruited, data or samples collected, and procedures performed. (max 100 words)	