APPLICATION OF THE JOINT MODELLING OF SERIAL ANTHROPOMETRIC MEASURES AND MORTALITY AMONGST CHILDREN FOLLOWING HOSPITALIZATION WITH A COINCIDENT ACUTE INFECTIOUS DISEASE IN ADDITION TO SEVERE ACUTE MALNUTRITION

VICTOR BENEFIT NYAWANGA

A thesis submitted in partial fulfillment of the requirements for the Degree of Master of Science in Statistics of Pwani University

August, 2016

DECLARATION

I declare that this thesis is my original work and has not been presented in any other university/institution for consideration of any certification. This thesis has been complemented by referenced sources duly acknowledged.

Victor Benefit Nyawanga

Registration number: I56/PU/3092/14

Department: Mathematics and Computer Science

Signature……Date…11-05-2017…

Supervisors' Declaration

We confirm that the work reported in this thesis was carried out by the candidate under our supervision.

DR. Leonard Kiti Alii

Pwani University

Lecturer, department of Mathematics and Computer Science

Signature……Date…11/05/2017…

Prof. Greg Fegan

Professor of Clinical Trials and Director

Swansea Trials Unit

Swansea University

Signature…G W Fegan…Date…11/5/2017…

DEDICATION

Dedicated to D.O.N…the best father in the world.

ACKNOWLEDGMENT

First, I give thanks to God for giving me good health and strength to write my thesis. Without His grace I would not have made it.

I thank my supervisors Dr. Leonard Kiti Alii and Prof. Greg Fegan for their time, input and unending support. The late night emails and early morning meetings have paid off!

I express my gratitude to my parents for their prayers and support, my siblings for their encouragement, my classmates for all their help and input and Stellah Mutuah and Ken Mwai for all their guidance. Philip Njenga, thanks for the lifts to school and the cups of coffee.

I gratefully acknowledge the financial support from Agnes Shikalo and Hawah Wangara without which my dream to have a masters degree would never have been realized.

To my beautiful wife and awesome daughter, no words can describe how thankful I am to you. This is for you!

ABSTRACT

Background: Malnutrition continues to be a major health burden in developing countries. It is globally the most important risk factor for illness and death, with hundreds of millions of young children particularly affected. The mid-upper arm circumference (MUAC) and the standardized weight-for- length Z-score (WFLz) are two anthropometric measures that are used for the diagnosis of malnutrition. The two anthropometric measures have poor correlation in terms of their predictive capabilities.

Design: A joint model was applied to data collected recently in a randomized, double blind, placebo-controlled trial to see which of these two anthropometric measures would be the better predictor of mortality in infants who were admitted to hospital with severe acute malnutrition and later discharged and followed up for one year. Typically longitudinal measures and event time data are modelled jointly by introducing shared random effects or by considering conditional distributions together with marginal distributions.

Participants: The study population comprised of 1781 children admitted to hospital with evidence of an acute infectious disease and with severe malnutrition and who had care initiated and were stabilized.

Results: Joint modelling showed that While WFLz was not significantly associated with mortality (p=0.202); MUAC had a high association with mortality (p=0.014) and was a predictor of children at risk of post-discharge mortality.

Conclusion: Using joint modelling approach, MUAC was identified as superior predictor of mortality amongst children treated for complicated SAM.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

1.0 Introduction

In some clinical studies, patients can be followed over a period of time, allowing for exposure measures to be serially recorded at multiple time points. The outcome of interest can be relapse of a disease, re-hospitalization or death, amongst others. A frequently encountered example of the latter case can be found in biomarker research, where clinical studies are designed to identify biomarkers with strong prognostic capabilities for survival time. The research questions in such studies often require separate analysis of recorded outcomes, but in many occasions interest may lie in studying the association of the biomarker and time-to-event, Rizopoulos (2012). When the interest is on the latter case, then joint modeling of the longitudinal and time-to-event method is adopted. Examples include, human immunodeficiency virus (HIV) research in which a researcher could be interested in the association between CD4 cell counts and the time to Acquired Immune Deficiency Syndrome (AIDS), liver cirrhosis studies which investigate the association between serum bilirubin and the time to death, systolic blood pressure and a coronary event, prostate-specific antigen biomarker and prostate cancer recurrence, and hemoglobin, specifically HbA1c, levels and survival in type 2 diabetes, Zhang et al (2009), Proust-Lima, and Taylor (2009). An important characteristic of medical conditions is their dynamic nature, that is, the rate of progression is not only different across patients but also dynamically changes in time within the same patient. This implies that the "true" potential of a biomarker in describing disease progression and its association with survival may only be revealed when repeated evaluations of the marker are considered together in analysis, Rizopoulos (2012). Joint modeling aims to answer such research questions involving the association structure between repeated measures and time to the event of interest. Joint modeling has been an active area of methodological research in the recent past, with one of the interests being dynamic predictions for either the survival or the longitudinal outcome, Rizopoulos (2012). The quality of this prediction

typically depends on the capability of the longitudinal marker itself in predicting future events, that is, the biological mechanism that the marker attempts to describe, and how strongly this mechanism is related to the event of interest.

As suggested by Black et al (2003) and Bryce et al (2005), malnutrition is a major problem in itself and also the most important risk factor for childhood death in developing countries. Severe acute malnutrition (SAM) is defined by the World Health Organization (WHO) and the United Nation's Children Education Fund (UNICEF) by a weight-for-length index of less than -3 z-score or a mid-upper arm circumference (MUAC) less than 115 mm, World Health Organization (1999). Severe acute malnutrition contributes to one million childhood deaths annually and complicated SAM is associated with high inpatient mortality rates, Brewster (2011). Inadequate attention to post-discharge issues has adverse implications because the available evidence suggests that in developing countries post-discharge deaths may be of similar (or higher) magnitude than inpatient deaths. A recent study conducted to explore excess pediatric mortality after discharge from Kilifi County Hospital found that child mortality was more than seven-fold higher among post-discharge children than among similarly-aged children in the community and that 4.5% of children who were discharged from hospital died within the subsequent year, Moisi et al (2011).

Mid-upper-arm-circumference (MUAC) and the standardized weight-for-length Z-score (WFLz) are two anthropometric markers used in the assessment of nutritional status. For infants between 0 and 60 months, the World Health Organization (WHO) recommends the use of WFL*z* to define wasting, since it is independent of stunting in its description for wasting while MUAC is increasingly being recommended to field operations as the indicator of choice for screening and admission to community-based management of acute malnutrition (CMAM) programs Guevarra et al (2012).. The commonly used thresholds for global acute malnutrition (GAM) are WFL*z*< -2 or MUAC < 125 mm.

These two indicators (WFLz and MUAC) correlate poorly with only about 40 % of SAM cases identified by one indicator also diagnosed as such by the other World Health Organization (2009). For example, among severely malnourished children hospitalized in rural Kenya, 65.1 % of the WFL*z* −3 cases also had a MUAC < 115 mm, whereas 56 % of the MUAC < 115 cases were also identified by WFL*z* −3. In that study, 42.9 % of the SAM cases were identified by both indicators, Berkley et al (2005). Fernandez et al.(2010) reported that among 34,937 children between 6 and 59 months from 39 nutritional surveys, 75 % of the children with a WFLz <−3 did not have a MUAC < 115 mm.

This study explored the post-discharge survival of children enrolled in a randomized controlled trial, Berkley et al. (2016), who were admitted to hospital with severe acute malnutrition, looking at their serial anthropometric measures and how these associate with mortality as a means of identifying infants at increased risk of post-discharge mortality.

1.1 Problem Statement

Malnutrition is a significant problem in developing countries and a strong risk factor for admission to hospital and death, Bryce et al. (2005). The two most commonly used anthropometric markers in the assessment of malnutrition (MUAC and WFLz) have very poor correlation in terms of predicting which infants are at risk of post discharge mortality due to malnutrition. This research aims to apply joint modelling to determine which of these two biomarkers is the more accurate and better predictor of children at risk of mortality due to malnutrition.

1.2 Justification

The two anthropometric markers that were being considered have poor correlation in terms of their predictive capabilities. This research aimed to apply joint modelling to determine which of the two anthropometric biomarkers is the better predictor of mortality. If a better predictor

is found, it can be translated as the standard tool in diagnosis of malnutrition and result in the reduction of mortality in infants with malnutrition.

1.3 Null Hypotheses

No difference in the predictive capability of the two anthropometric markers of malnutrition.

1.4 Objective of the study

The objective of this study was to create a joint model of serial anthropometric measures (MUAC and WFLz) and mortality. This model could possibly tell us which of the two anthropometric markers the better predictor of mortality in infants.

1.5 Specific Objectives

I. To determine the association between the anthropometric indicators (MUAC and WFLz) with mortality in children with severe acute malnutrition.

II. To investigate the predictive capabilities of MUAC and WFLz on mortality.

III. To determine which of the two anthropometric indicators (MUAC and WFLz) is the better predictor of mortality in children with severe acute malnutrition.

CHAPTER 2: LITEARTURE REVIEW

2.0 Anthropometry and malnutrition

For infants aged between 0 and 60 months, World Health Organization (WHO) recommends the use of WFL*z* to define wasting, World Health Organization (1999). A WFL*z* lower than −3 standard deviations of the international reference population can be used as an indicator of SAM, World Health Organization (2009). Mid-upper arm circumference has also been endorsed by the WHO, the World Food Programme (WFP), the United Nations System Standing Committee on Nutrition (SCN) and the United Nations Children's Fund (UNICEF) as a suitable tool for diagnosing severe acute malnutrition (wasting) and as criteria for admission into therapeutic feeding programs, World Health Organization (1999). Many agencies are beginning to move towards using MUAC as a basis for admitting children to both therapeutic and supplementary feeding programs, Myatt et al. (2008). A study by Mwangome et al (2012) showed that MUAC was a more reliable marker in determining children aged between 6-14 weeks who are at elevated risk of death as compared to WFLz. These two anthropometric measurements are critical tools in predicting death and can be used as timely indicators to allow for early intervention.

2.1 Post-discharge mortality

A recent study conducted in Bangladesh reported high mortality within 3 months of discharge of Bangladeshi children following hospitalization with severe malnutrition and pneumonia. The reported post-discharge mortality of 8.7% was similar to the inpatient mortality. Most of the post-discharge deaths occurred within 1 month following discharge Chisti et al. (2014).Another study that included 393 HIV-uninfected Malawian children with severe malnutrition, reported 44 (11%) deaths within 3 months, Kerac et al. (2009). A study conducted to explore excess pediatric mortality after discharge from Kilifi County Hospital found that child mortality was more than seven-fold higher among post-discharge children

than among similarly-aged children in the community and that 4.5% of children who were discharged from hospital died within the subsequent year, Moisi J., Gatakaa H.. and Berkley J. (2011).

2.2 Joint modelling

Joint modelling is used to estimate the association between survival times and endogenous time-dependent covariates. The longitudinal outcomes (biomarkers or other serial measures) are referred to as endogenous time-dependent covariates in a survival modelling framework. Important features of endogenous time-dependent covariates are: (1) they require survival of the patient for them to exist, (2) they are measured with error and (3) their complete path up to any time *t* is not fully observed, that is, the marker of the patient is only known at days when the patients provide the measurements, Rizopoulos (2012). When primary interest is in the association between such endogenous time-dependent covariates and survival, a modeling framework has been introduced, known as the joint modeling framework for longitudinal and time-to-event data, Faucett and Thomas (1996) and Tsiatis and Davidian (2004).

The idea behind joint models is to combine two sub-models, a survival model and a suitable model for the repeated measurements that will account for its special features. The sub-models are specified below, specifically with regards to the approach of Prof Dimitris Rizopoulos as shown in Rizopoulos (2012).

To assist in introducing this modeling framework, some notations will be used. The true event time for the i^{th} subject will be denoted by T_i^*, T_i will denote the observed event time, defined as the minimum of the potential censoring time C_i and T_i^*, and by $\delta_i = I(T_i^* \leq C_i)$ the event indicator. For the endogenous time-dependent covariates, let $y_i(t)$ denote its observed value at time point *t* for the i^{th} subject. It should be noted that $y_i(t)$ is not observed for any time *t*, but rather only at the very specific occasions t_{ij} at which measurements were taken. Thus, the observed longitudinal data consist of the measurements $y_{ij} = \{y_i(t_{ij}), j = 1, \dots, n_i\}$.

2.3 Survival sub model

A new term $m_i(t)$ that denotes the true and unobserved value of the longitudinal outcome at time t is introduced. Note that $m_i(t)$ is different from $y_i(t)$, with the latter having measurement error value of the longitudinal outcome at time t. To quantify the strength of the association between $m_i(t)$ and the risk for an event, a straight forward approach is to postulate a relative risk model of the form:

$$\lambda_i(t|\mathcal{M}_i(t), \omega_i) = \lambda_0(t)\exp\{\gamma^T\omega_i + \alpha m_i(t)\} t > 0 \qquad (2.3.1)$$

Where $m_i(t) = \{m_i(s), 0 \leq s < t\}$ is the history of the true but unobserved longitudinal process up to time point t, $\lambda_0(.)$ is the baseline risk function and α is the parameter representing the longitudinal effect on hazard. Similarly, ω_i is a vector of baseline covariates associated with parameter vector γ. The risk for an event at time t therefore depends on the baseline hazard, baseline covariates and the true value of the longitudinal covariate at that time. The risk ratio associated with unit changes of baseline covariates is given by $\exp(\gamma)$ and the relative change in the risk for a unit change in the true value of the longitudinal covariate is $\exp(\alpha)$, Rizopoulos (2011).

2.4 Longitudinal sub-model

In the above definition of the survival model, the true unobserved value of the longitudinal covariate $m_i(t)$ was used. Taking into account that the longitudinal information $y_i(t)$ is collected with possible measurement errors, the first step towards measuring the effect of the longitudinal covariate to the risk for an event is to estimate $m_i(t)$, in order to reconstruct the complete true history $m_i(t)$ for each subject. Then, the linear mixed model can be rewritten as,

$$\begin{cases} y_i(t) = m_i(t) + u_i(t) + \epsilon_i(t), \\ m_i = x_i^T\beta + z_i^T b_i, \\ \qquad b_i \sim N(0, D) \\ \epsilon_i \sim N(0, \sigma^2 I_{ni}) \end{cases} \qquad (2.4.1)$$

This mixed model formulation allows one to state that the longitudinal outcome $y_i(t)$is equal to the true level $m_i(t)$ plus an error term. An incorporated stochastic term $u_i(t)$ can be added. This term is used to capture the remaining serial correlation in the observed measurements, which random effects are unable to capture. Considering that $u_i(t)$ is considered as a mean-zero stochastic process, independent of $b_i$and ϵ_i.

The equation is a linear mixed model which accounts for measurement error problems by postulating that the observed level of longitudinal outcome $y_i(t)$ comprises of true value $m_i(t)$ and a random error term,$\epsilon_i(t)$. If observations are taken on a regular basis, it is improper to disregard autocorrelation. However, it is difficult to implement a model with both random-effects and autocorrelation term, Tsiatis and Davidian (2004), therefore a random-effects model was preferred due to its computational ease in implementation. By fitting the linear mixed submodel, the true biomarker value is estimated and the complete patient's longitudinal history $m_i(t)$ is reconstructed.

Statistical models are often built to provide predictions. When good quality predictions are of interest, it would be useful to combine all available information available for a patient in order to account for the biological interrelationships between the outcomes. The importance of combining serial sets of markers for prediction was empirically illustrated by Fieuws et al (2008), who noted that predictions of graft failure in a kidney transplant study based on a joint model using all recorded biomarkers of kidney functioning provided better predictions (in terms of early detection of patients at risk of renal graft failure), than those provided by separate analysis per marker.

CHAPTER 3: MATERIALS AND METHODS

3.0 Study sites

The trial was carried out at four sites, Coast Provincial General Hospital, Kilifi County Hospital, Malindi Sub-County Hospital and Mbagathi District Hospital.

3.1 Study design

The data used for this study came from a multicentre, double-blind, randomized, placebo-controlled trial. In such a trial of a medical treatment, some (roughly half) of the participants are given the treatment, in this case Co-trimoxazole (CTX), others are given fake treatment (placebo), and neither the researchers nor the participants know in which arm of the study they were until the study ends (they are thus both “blind”).

3.2 Demographic details

Kilifi County Hospital serves a rural population the majority of who are farmers. Malindi Sub-County Hospital is within Kilifi County approximately 60km North of Kilifi town. It mainly serves a rural population that lives in a semi-arid area to the West and North to the border with Lamu District and also Malindi Town. Sixty eight percent of Kilifi District residents and 76% of Malindi District residents were estimated to live below the national poverty line in 2006.Coast Provincial General Hospital is the largest provincial hospital in Kenya and predominantly serves residents of Mombasa Town plus referrals from the entire coast region. Thirty eight percent of Mombasa District residents were estimated to live below the national poverty line in 2006. Mbagathi District Hospital is located near the Kibera informal settlement in Nairobi and serves populations living in informal settlements across the entire Nairobi region. In 2006, 38% of Nairobi District residents were estimated to live below the national poverty line.

3.3 Study population

The study population comprised of children admitted to hospital with evidence of an acute infectious disease and with severe malnutrition and who had care initiated and were stabilized.

3.4 Inclusion Criteria:

Patients who were considered for the trial were aged between 2 months and 5 years. They had to have been diagnosed with severe malnutrition (severe malnutrition defined as: age 6 months to 5 years: MUAC <11.5cm; age 2 to 6 months: MUAC <11cm) or kwashiorkor at any age (defined in current WHO guidelines (World Health Organization (2005)). A negative HIV rapid test or if under 18 months, HIV-1 PCR negative and no longer breastfeeding for at least 6 weeks. Potential participants should have been willing to remain within study area and come for all protocol specified visits.

3.5 Apparatus and/or Instruments

All children admitted to the study were weighed using an electronic scale (Seca 825, Birmingham UK) to 0.01 kg. Length was measured to 0.1 cm using an infantometer (Seca 416, Birmingham UK) or stadiometer (Seca 215, Birmingham UK). Mid upper arm circumference was measured to 0.1m cm using a standard insertion tape (TALC, St. Albans, UK). Kwashiorkor was diagnosed on the basis of bilateral pitting pedal oedema, World Health Organization (2005).

3.6 Data

The data was collected by KEMRI-Wellcome Trust, Kilifi and entered into OpenClinica, Ngari et al (2014). The aim of the trial for which this data was collected was to find out whether daily cotrimoxazole prophylaxis could reduce mortality among severely malnourished children who are not infected with HIV, Berkley et al. (2016). The data was collected at two rural and to urban hospitals between November 2009 and March 2014. One thousand seven hundred and eighty one patients were recruited into the study. Follow-up was done on a monthly basis for six months after discharge from hospital and thereafter every

other month up to one year. However, for this study, the data was limited to the subset of the first six-month period when children were on daily prophylaxis. In addition to the serial anthropometric measurements (WFLz and MUAC), the baseline covariates that were recorded were age, gender, pneumonia, diarrhea and oedema.

3.7 Estimation in joint modelling

Self and Pawitan proposed a joint model with a relative risk submodel of the form

$$h_{\mathrm{i}}(t|M_{\mathrm{i}}(t), w_{\mathrm{i}}) = \lim_{dt\to 0} \Pr\{t \le T_i^* < t + dt | T_i^* \ge t, M_{\mathrm{i}}(t), w_{\mathrm{i}}\}/dt$$

$$= h_0(t)\exp\{\gamma^T \omega_i + \alpha m_i(t)\} t > 0 \qquad (3.7.1)$$

with an unspecified baseline risk function $h_0(t)$, and with the term exp $\{\alpha m_i(t)\}$ replaced by $\{1+ \alpha m_i(t)\}$, such that the model would be linear in the random effects b_{i}. The authors proposed to estimate this joint model using a two-step inferential approach, in which at step one the random effects are estimated using a least-squares approach, and at step two these estimates are used to impute appropriate values of $M_{\mathrm{i}}(t)$ that are substituted in the classical partial likelihood of the Cox model, Ye et al. (2008) Even though these approaches are relatively easy to implement with standard software, in many instances they produce biased results. This has been shown with a series of simulations studies, Henderson, Diggle, and Dobson (2000). For this reason and instead of relying on approximations, the literature for this type of joint models has primarily focused on full likelihood approaches that eliminate this bias.

The main estimation method that has been proposed for joint models is (semi parametric) maximum likelihood, Hsieh et al (2006). Moreover, Tsiatis and Davidian proposed a conditional score approach in which the random effects are treated as nuisance parameters, and they developed a set of unbiased estimating equations that yields consistent and asymptotically normal estimators, Lipsitz, S., Fitzmaurice, G., Ibrahim, J., Gelber, R., and Lipshultz, S. (2002)

The maximum likelihood estimates are derived as the modes of the log-likelihood function corresponding to the joint distribution of the observed outcomes. To define this joint distribution we will assume that the vector of time-independent random effects b_i underlies both the longitudinal and survival processes. This means that these random effects account for both the association between the longitudinal and event outcomes, and the correlation between the repeated measurements in the longitudinal process (conditional independence). Formally, we have that

$$p(T_i, \delta_i, y_i|b_i; \theta) = p(T_i, \delta_i|b_i; \theta)\, p(y_i|b_i; \theta) \text{ and}$$

$$p(y_i|b_i; \theta) = \prod_j p\{y_i(t_{ji}|\, b_i; \theta\} \qquad (3.7.2)$$

Where $\theta = (\theta_t^\tau, \theta_y^\tau, \theta_b^\tau)^\tau$ denotes the full parameter vector, with θ_t denoting the parameters for the event time outcome, θ_y the parameters for the longitudinal outcomes and θ_b the unique parameters of the random-effects covariance matrix, and y_i is the $n_i \times 1$ vector of longitudinal responses of the i^{th} subject. In addition, it is assumed that given the observed history, the censoring mechanism and the visiting process are independent of the true event times and future longitudinal measurements. As defined earlier, the visiting process is the mechanism (stochastic or deterministic) that generates the time points at which longitudinal measurements are collected, Lipsitz et al (2002), and for any time point *t*, define as observed history all available information for the longitudinal process prior to *t*. Practically speaking, these assumptions imply the belief that decisions on whether a subject withdraws from the study or appears at the clinic for a longitudinal measurement depend on the observed past history (longitudinal measurements and baseline covariates), but there is no additional dependence on underlying, latent subject characteristics associated with prognosis.

Under these assumptions the log-likelihood contribution for the i^{th} subject can be formulated as follows

$$\log p(T_i, \delta_i, y_i; \theta) = \log \int p(T_i, \delta_i, y_i, b_i; \theta) db_i$$

$$= \log p(T_i, \delta_i | b_i; \theta, \beta) \left[\prod_j p\{y_i(t_{ji}) | b_i; \theta y\}\right] p(b_i; \theta) db_i \quad (3.7.3)$$

with the conditional density for the survival part $\log p(T_i, \delta_i | b_i; \theta, \beta)$ taking the form

$$p(T_i, \delta_i | b_i; \theta, \beta) = h_i(T_i | M_i(T_i)\theta_i, \beta)^{\delta_i} S_i(T_i | M_i(T_i)\theta_i, \beta)$$

$$= [h_0(T_i)\exp\{\gamma^T \omega_i + \alpha m_i(T_i)\}]^{\delta_i} \times \exp\left(-\int_0^{T_i} h_0(s)\exp\{\gamma^T \omega_i + \alpha m_i(s)\} ds\right)$$

(3.7.4)

where $h_0(\cdot)$ can be any positive function of time, such as the piecewise-constant model below

$$h_0(t) = \sum_{q=1}^{Q} ב_q I(v_{q-1} < t < v_q) \quad (3.7.5)$$

where $0 = v_0 < v_1 < v_2 < \cdots < v_q$ denotes a split of the time scale, with v_0 being larger than the largest observed time, and $ב_q$ denotes the value of the hazard in the interval $[v_{q-1}, v_q]$.

$h_0(\cdot)$ can also be a positive function of the B-spline model below

$$h_0(t) = \kappa_0 + \sum_{d=1}^{m} \kappa_d B_d(t, q) \quad (3.7.6)$$

where $\kappa^\tau = \kappa_0, \kappa_{1,\cdots,}\kappa_m$ are the spline coefficients, q denotes the degree of the B-splines basis functions $B(\cdot)$, and, with $m = \ddot{m} + q - 1$ with $\ddot{m}$ denoting the number of interior knots.

$h_0(\cdot)$ can also be the hazard function of any known distribution, and the survival function is given by the equation below

$$S_i(t | M_i(t), w_i) = \Pr(T_i^* > t | M_i(t), w_i)$$

$$= \exp\left(-\int_0^t h_0(s)\exp\{\gamma^T \omega_i + \alpha m_i(s)\} ds\right) \quad (3.7.7)$$

The joint density for the longitudinal responses together with the random effects is given by the equation below

$$p(y_i|b_i;\theta)p(b_i;\theta) = \prod_j p\{y_i(t_{ij})|\, b_i;\theta_y\}p(b_i;\theta_b) \qquad (3.7.8)$$

$$= (2\pi\sigma^2)^{-n_i/2}\exp\{-||y_i - X_i\beta - Z_i b_i||^2/2\sigma^2\} \times (2\pi)^{-\frac{q_b}{2}}\det(\mathrm{D})^{-\frac{1}{2}}\exp(-b_i^\tau D^{-1}b_i/2)$$

Where q_b denotes the dimensionality of the random-effects vector, and $\| x \| = \{\sum_i x_i^2\}$ denotes the Euclidean vector norm.

3.8 Data analysis

The data was analyzed using the R, R Core Team (2015), (version 3.2.3) statistical environment, with the joint modelling done using JM package, Rizopoulos (2010). R was chosen due to its simple, powerful and dynamic nature. In addition, the joint model that was fit used the same approach to that used by Dimitris Rizopoulos, who has implemented a number of joint modelling packages in R, Rizopoulos (2010) and Rizopoulos (2011).

3.9 Joint modeling methodology

For the time after discharge from hospital and for each of the longitudinal measures separately, a joint model was fitted. The basic model (assuming risk is dependent on the current value of the measure) was built in two stages. In stage one, the linear predictor of the survival sub-model only contained the effect of the measure. The sub-model was fitted with Weibull baseline hazard model. The fixed effects structure of the longitudinal sub-model only included the time evolution while the random structure had random slope and intercept. In stage two, the baseline covariates were added one by one in both the longitudinal and survival sub-models. The likelihood ratio test was used to test if the covariate was important or not at the 5% significance level. The longitudinal and survival sub-models were combined to create the final the joint model. The joint models were then compared to see which would give a better prediction of the event of interest. This was achieved by comparing them using Akaike's information criterion (AIC), Akaike (1974), calculated as:

$$AIC = -2 \times loglikelihood + 2k$$

Where k is the number of parameters in the fitted model. This criterion finds balance between accuracy and complexity of the fitted model. The model with the smallest AIC is considered as the better predictor and is the preferred model.

To improve the numerical stability of the models, the covariates were rescaled to unit magnitude by dividing each measure by the maximum value for that measure.

For the WFLz, the basic longitudinal submodel (linear mixed effects model) was written as follows

$$WFLz_i(t) = M_i(t) + \varepsilon_i(t)$$

$$= \beta_0 + \beta_1(t) + b_{i0} + b_{i1}t + \varepsilon_i(t) \qquad (3.9.1)$$

In the fixed-effects part we include the main effect of time and in the random-effects design matrix we include an intercept and a time term. A joint model of the following form was then fit.

$$h_i(t) = h_0(t)\exp\{\gamma \aleph_i + \alpha M_i(t)\} \qquad (3.9.2)$$

Where $\aleph_i$ represents the baseline covariates. The above equation can thus be expanded to be of the form

$$h_i(t) = h_0(t)\exp\{\gamma_1 Pneumonia + \gamma_2 Diarrhea + \gamma_3 Age + \gamma_4 Treatment + \alpha M_i(t)\}$$

(3.9.3)

CHAPTER 4: RESULTS

4.1 Exploratory data analysis

One thousand seven hundred and eighty one children were enrolled in the four sites. Coast general hospital in Mombasa County enrolled 849 children. Kilifi county hospital enrolled 151 children. Malindi sub county hospital enrolled 271 children and Mbagathi hospital in Nairobi enrolled 507 children. All children at all the four sites were enrolled between 20/11/2009 and 28/03/2014. Three children were excluded as ineligible leaving one thousand seven hundred and seventy eight children were included in the analysis.

Eight hundred and eighty seven children were assigned to cotrimoxazole prophylaxis and eight hundred and ninety one assigned to placebo. Both longitudinal biomarkers had missing values. In addition, 126 patients had enrollment measurements but no post-discharge measurements. These patients were excluded from the analyses. The final analyses were thus done on 1652 patients.

The mean age at enrollment was 12.75 (SD=8.91, range 2-55) and the mean WFLz and MUAC at enrollment were -3.34 and 10.56 respectively. Nine hundred and six (50.8 %) of the study participants were male. Three hundred (16.8 %) had oedematous malnutrition and 1024 (57.5 %) were enrolled with diarrhea. Table 2(a) shows some selected baseline characteristics of children enrolled in the trial based on the serial anthropometric measures.

MUAC							
	Month 0	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
Diarrhea							
No	10.57	11.30	11.76	12.09	12.40	12.55	12.74
Yes	10.55	11.35	11.91	12.20	12.46	12.64	12.86
Pneumonia							
No	10.71	11.58	12.16	12.44	12.69	12.88	13.04
Yes	10.43	11.11	11.57	11.89	12.21	12.35	12.59
Sex							
Female	10.57	11.32	11.80	12.09	12.35	12.50	12.72
Male	10.54	11.34	11.89	12.21	12.51	12.70	12.88
WFLz							
Diarrhea							
No	-3.14	-2.40	-2.11	-1.84	-1.76	-1.72	-1.62
Yes	-3.38	-2.49	-1.96	-1.82	-1.65	-1.60	-1.47
Pneumonia							
No	-3.41	-2.29	-1.80	-1.62	-1.49	-1.41	-1.33
Yes	-3.21	-2.59	-2.22	-2.05	-1.88	-1.87	-1.73
Sex							
Female	-3.09	-2.30	-1.90	-1.73	-1.63	-1.55	-1.44
Male	-3.48	-2.50	-2.14	-1.95	-1.76	-1.74	-1.63

Table 2(a)*: selected baseline characteristics of study participants based on MUAC and WFLz*

The primary event of interest of this study was death. The distribution of the number of deaths (210 in total) over the six month study period was as follows: 123 in the first month, 32 in the second month, 21 in the third month, 19 in the fourth month, 9 in the fifth month and 6 in the

sixth month. This indicates a decreasing risk over time. An overall increase was observed in the values of the two anthropometric indicators. This is shown in table 2(b).

Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**
MUAC	10.56	11.33	11.85	12.15	12.44	12.61	12.81
WFLz	3.28	2.45	2.02	1.85	1.70	1.65	1.54
Deaths	-	123	32	21	19	9	6

***Table 2(b)**: the average monthly anthropometric values and distribution of deaths.*

To investigate survival probabilities by the different baseline covariates, Kaplan-Meier curves were plotted. Figure 1 shows a Kaplan-Meier survival estimate, with the 95% confidence interval, for the time to death of all study participants.

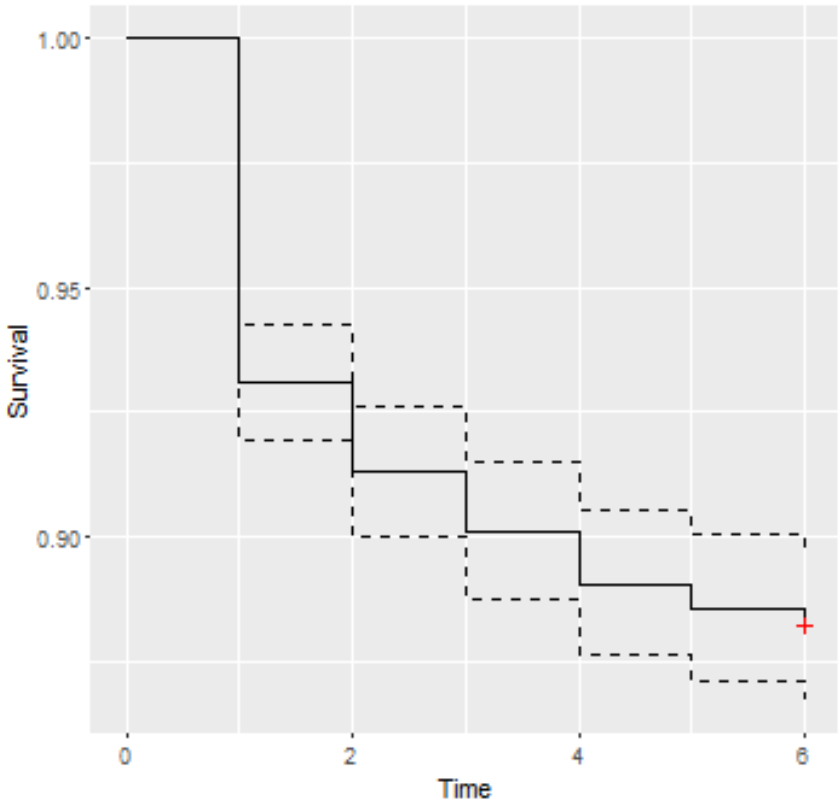

Figure 1: *Kaplan-Meier survival estimate for time to death*

Comparison of different pairs of survival curves was done using the log rank test. It tests the null hypothesis that there is no difference between the population survival curves (i.e. the probability of an event occurring at any time point is the same for each population).

From figure 1a it seemed that male and female children had a very small difference in survival probabilities. The log-rank test showed no significant difference existed between the two groups (p-value= 0.579).

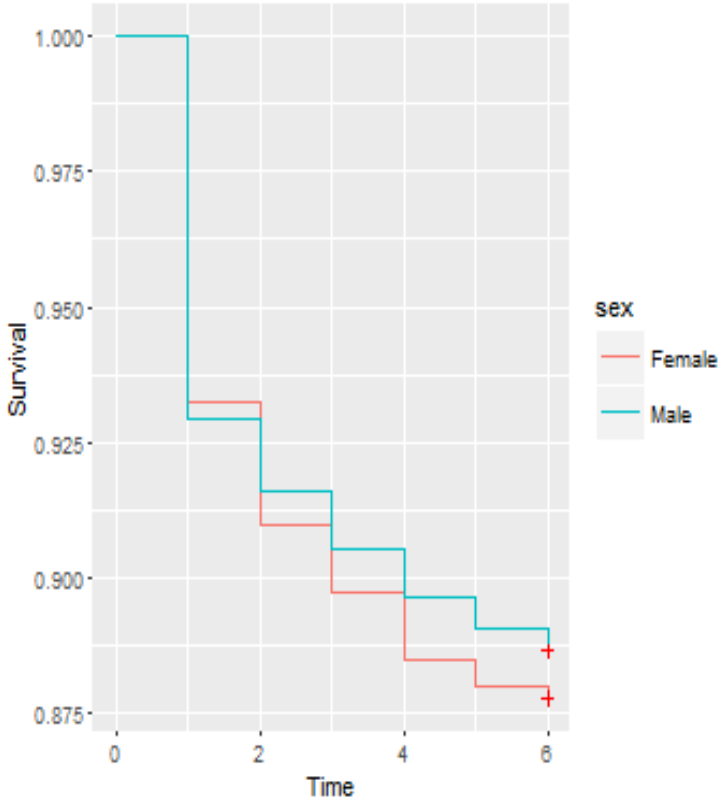

***Figure 1a**: KM by gender*

Figure 1b shows the survival curves of patients with diarrhea and without diarrhea. Patients with diarrhea at admission had a better survival probability than those without. The log-rank test showed this difference to be significant (p-value= 0.014)

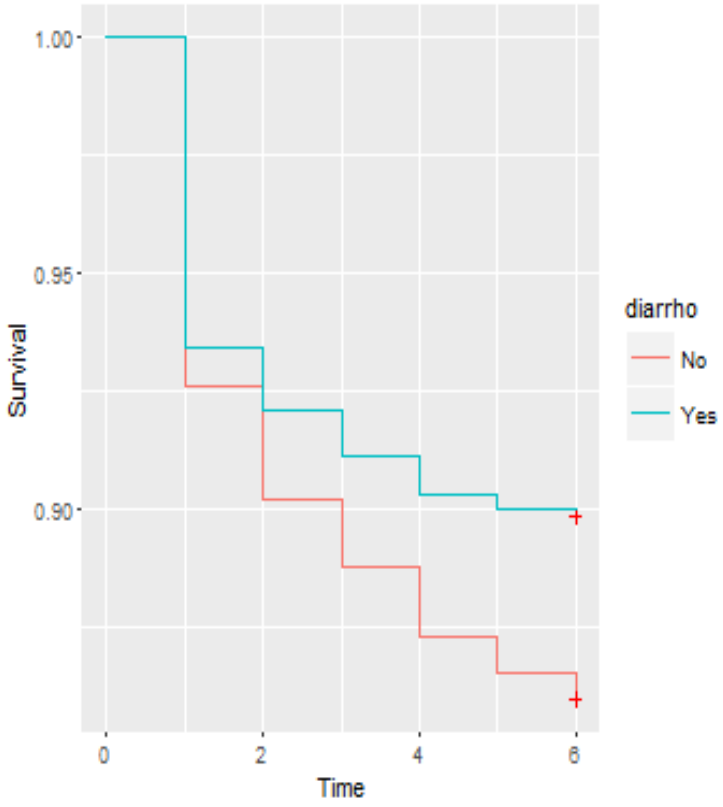

***Figure 1b**: KM by diarrhea*

Figure 2a suggests that there was no significant difference between patients placed on the different treatments. This implies that no significant difference existed in the survival of the patients on CTX ant those on placebo. This was confirmed by the log-rank test (p-value= 0.968).

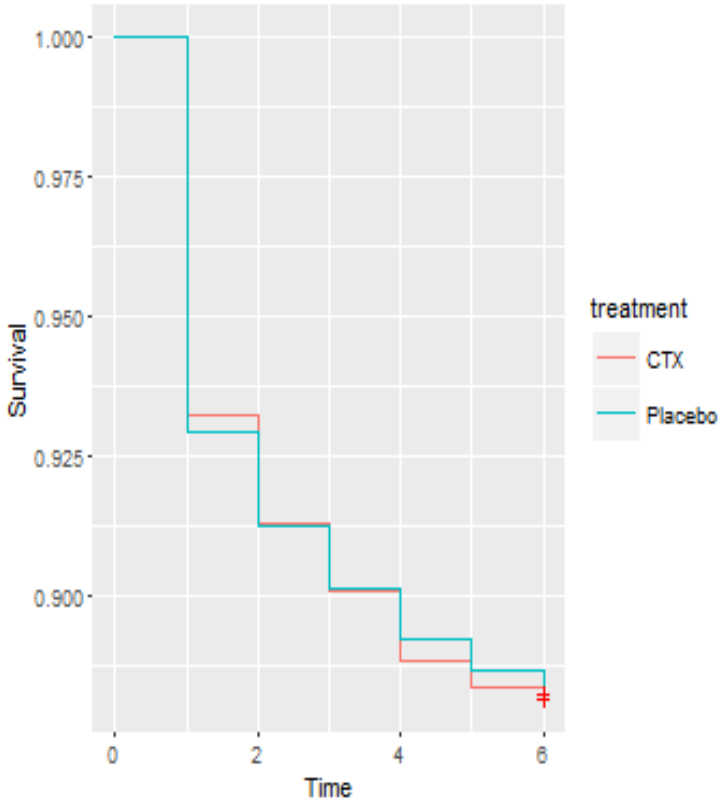

Figure 2a: *KM by treatment*

Figure 2b suggests a significant difference in the survival probability between study participant admitted with pneumonia and those admitted without pneumonia. The log-rank test indicates a highly significant difference in the survival probabilities of patients with pneumonia and those without pneumonia (p-value < 0.001). Patients without pneumonia had a higher survival probability than those with pneumonia.

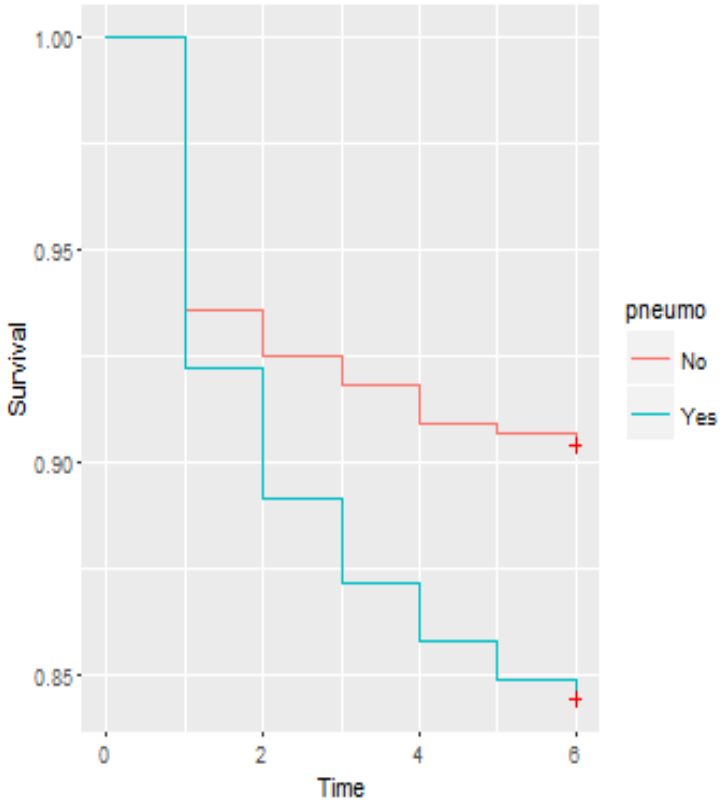

***Figure 2b**: KM by pneumonia*

Figure 3a shows a significant difference (log-rank test p-value = 0.026) in survival probability among the different sites. Patients enrolled in Kilifi county hospital seemed to have a better survival probability than their counterparts in the other sites.

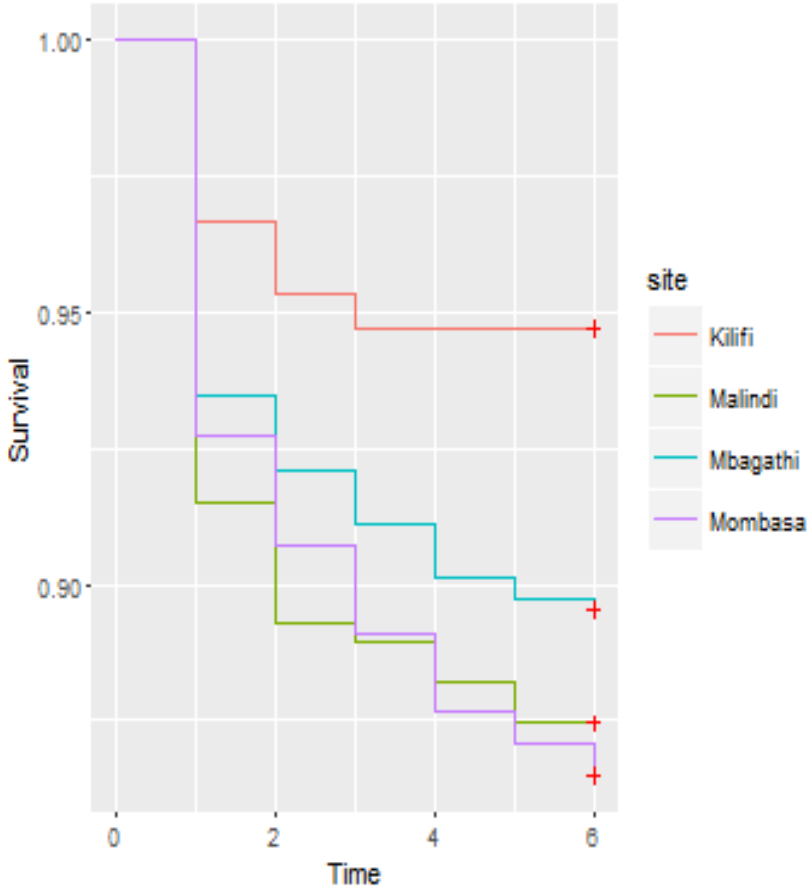

Figure 3a: *KM by site*

Figure 3b suggests that patients admitted with oedema would have a higher post-discharge survival probability than those admitted without oedema. Out of the total of 1781 patients, only 300 were admitted with oedema. Even though patients with oedema seem to have a higher survival probability, it is not statistically significant (log-rank test p-value = 0.071)

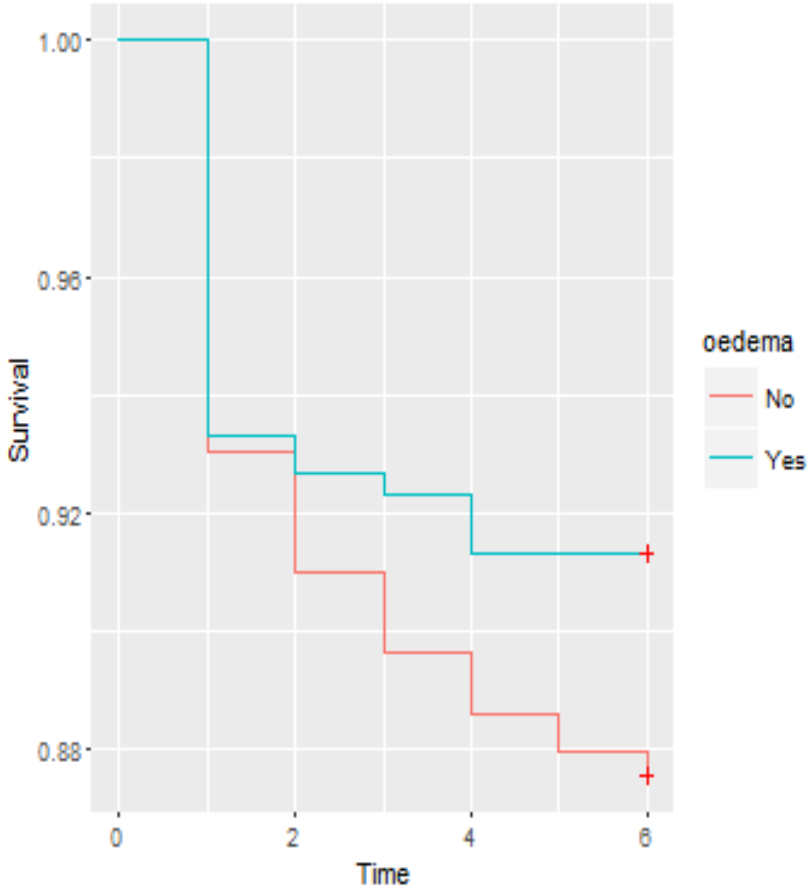

Figure 3b: *KM by* oedema

4.2 Weight for length z-score (WFLz)

4.2.1 Mean structure

Exploration of the mean structure was done using average profile plots. An overall as well as a different average profile for each of the different levels of the baseline covariates were plotted. From the average profile plot shown below in figure 4, an increasing trend was observed. A sharp increase is seen during the first two months after the patient was discharged from hospital.

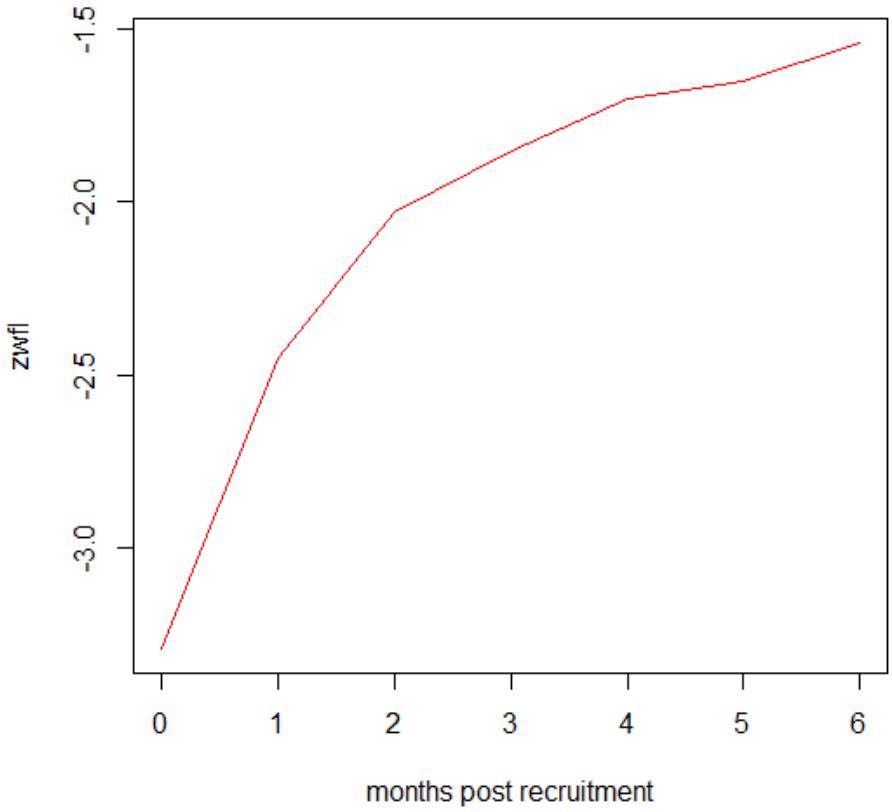

Figure 4: *WFLz mean structure*

On average, female patients had a higher WFLz than male patients as shown in figure 4a.

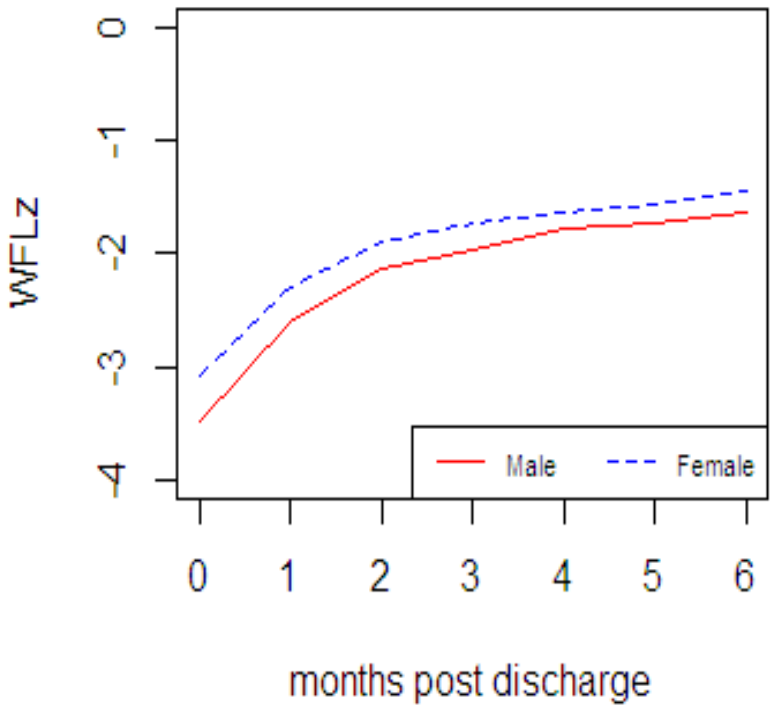

Figure 4a: *WFLz by gender*

Figure 4b suggests an insignificant difference in the mean WFLz between patients admitted with diarrhea and those without diarrhea. Figure 4c indicates that during the first month (post-discharge), the WFLz between patients with pneumonia and those without was insignificant. But as from the second month, the difference between the WFLz of the two groups starts increasing. A somewhat constant and significant difference is observed until the end of the study (month six).

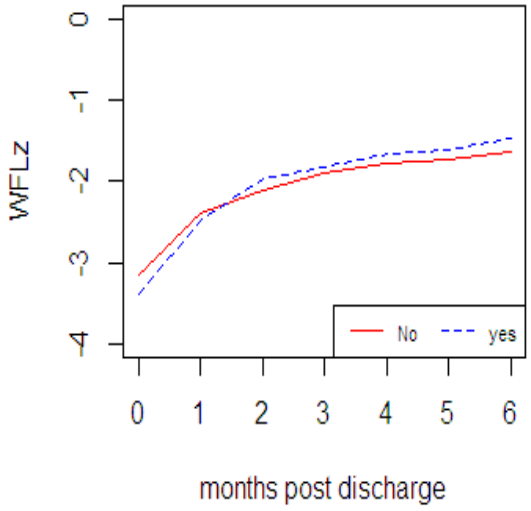

***Figure 4b**: WFLz by diarrhea*

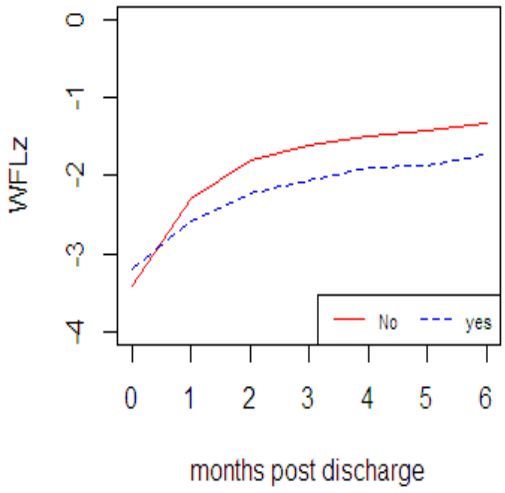

***Figure 4c:** WFLz by pneumonia*

Figure 4d shows the trends observed in the mean WFLz of the patients subjected to the different treatments (CTX and Placebo)

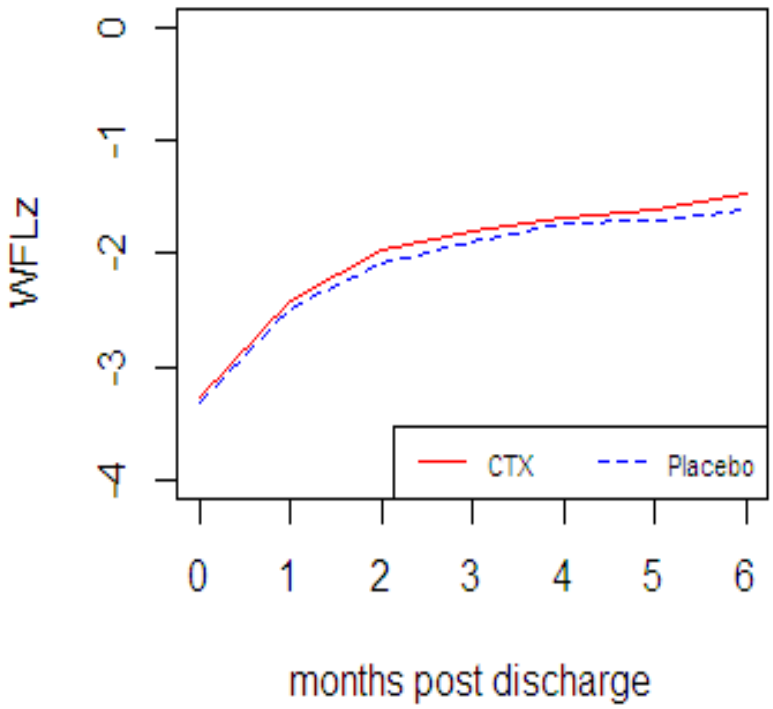

Figure 4d: *WFLz by treatment*

4.2.2 Variance Structure

The average evolution of the variance of WFLz as a function of time is shown in Figure 5. There is a sharp increase during the first month after discharge. After the first month the evolution of the variance of WFLz is fairly constant.

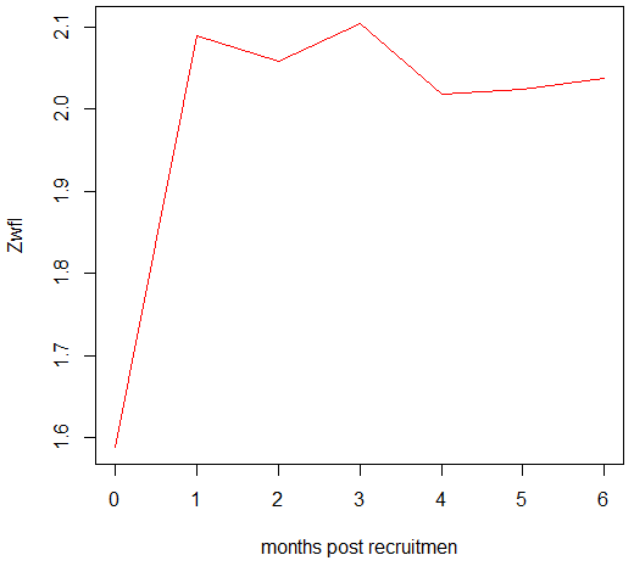

Figure 5: *WFLz Variance structure*

4.3 Mid upper arm circumference (MUAC)

4.3.1 Mean structure

From the overall average profile plot in figure 6, a general linear trend was observed.

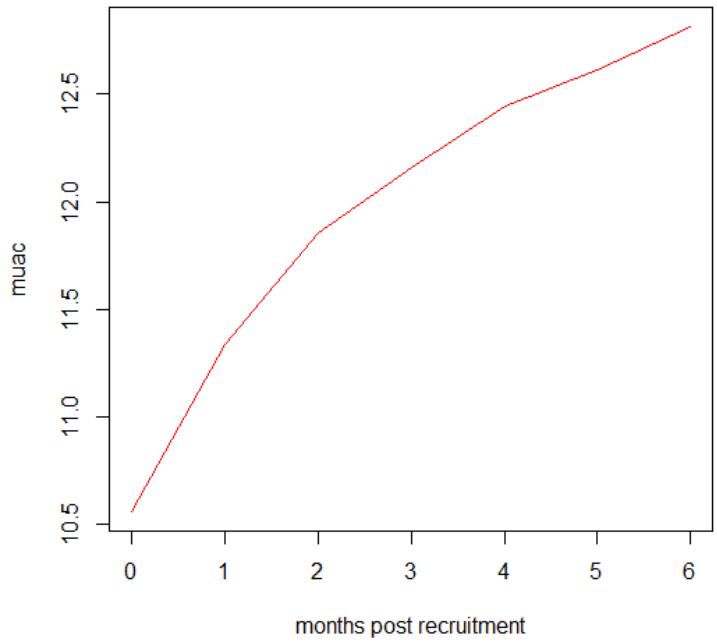

Figure 6: *MUAC Variable: Mean structure*

Figure 6a suggests that there was no significant difference between the average MUAC values in the patients admitted with diarrhea and those without diarrhea.

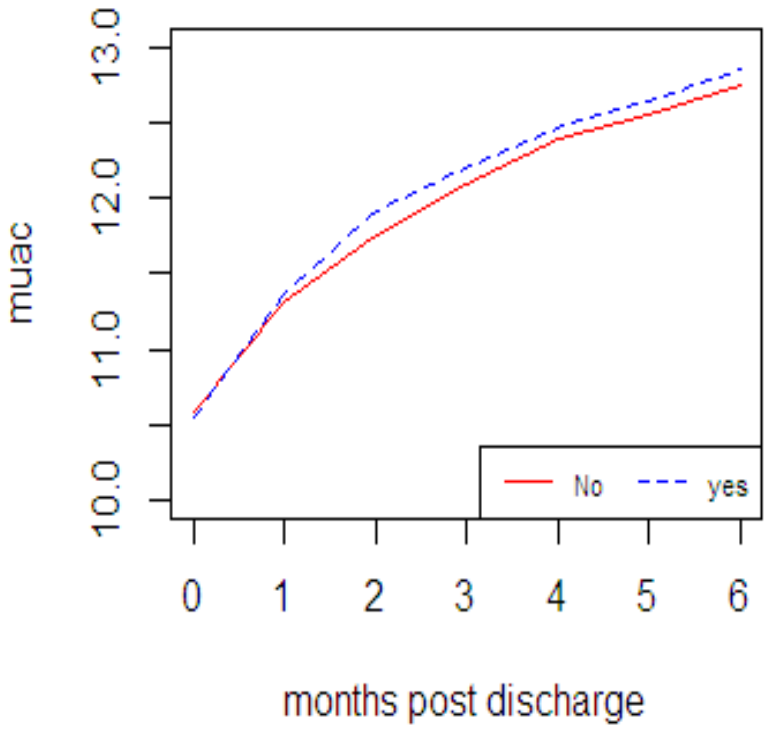

Figure 6a: *MUAC by diarrhea*

Figure 6b indicates that patients admitted with pneumonia had, on average, a lower MUAC as compared to their counterparts who were admitted without pneumonia. There was no difference in the average MUAC values of patients subjected to the different treatments. This is illustrated in figure 6c

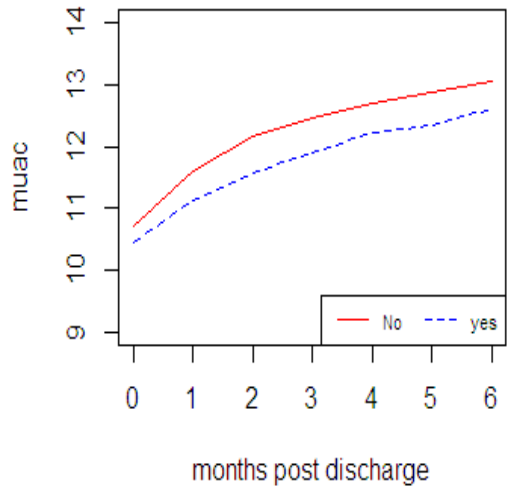

Figure 6b: ***MUAC by pneumonia***

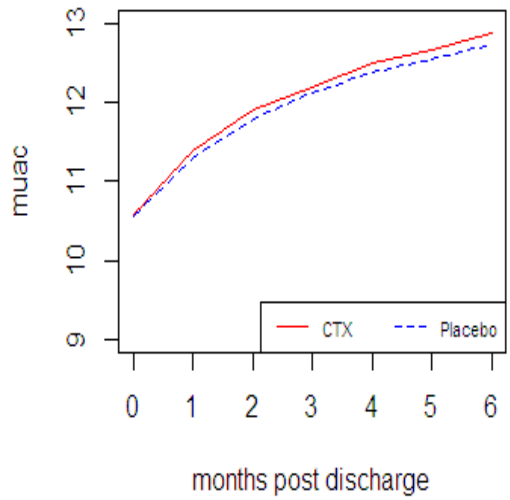

Figure 6c: *MUAC by treatment*

During the first month after discharge from hospital, there was no significant difference in the average MUAC values of males and females. This is shown on figure 6d.

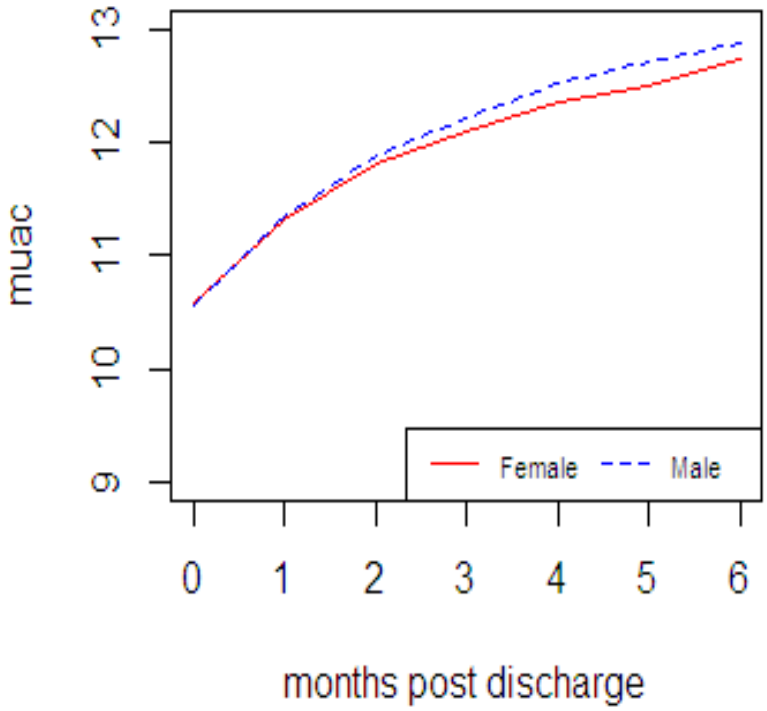

***Figure 6d**: MUAC by gender*

4.3.2 Variance structure

The average evolution of variance as function of time is shown in Figure 3(b). The general evolution of the variance function is not constant.

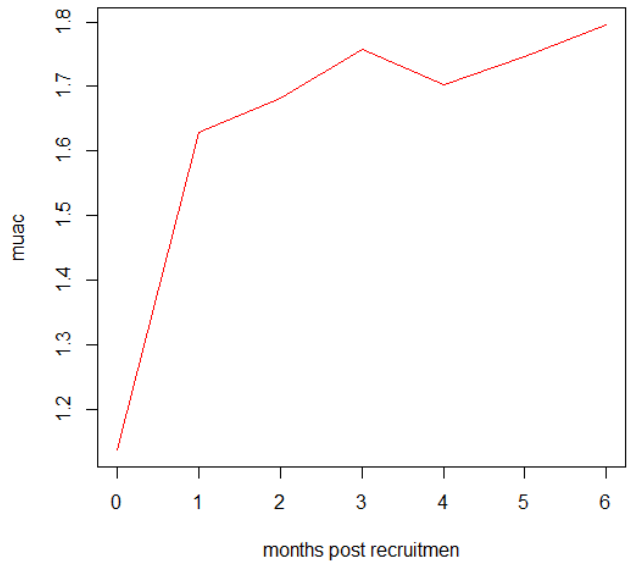

Figure 3(b): *MUAC Variable: Variance structure*

4.4 WFLz results

To start with, the basic survival submodel containing only WFLz as a covariate as described above was fitted. A likelihood ratio test was carried out at 5% level of significance to determine if any of the baseline covariates were significant. Treatment and site were found to be insignificant (p-value>0.05) while pneumonia (p-value=0.007), diarrhea (p-value=0.028) and age in months (p-value<0.001) were found to be significant. Site was dropped but treatment was retained in the model.

Initially the numerical integration was done using adaptive Gauss-Hermite rule with 15 points and then the points were gradually increased. Convergence was concluded when the parameter estimates and the AIC values were no longer changing. Analysis was conducted assuming a Weibull baseline hazard for the survival submodel.

The results of the model are presented in table 3. The parameter α in equation 1 is reported as the 'Assoct' in the results of the joint model. This parameter indicates how strongly our longitudinal biomarker (WFLz) is associated with the timing of the event of interest which is post-discharge death. The Assoct parameter has a p-value of 0.202 which is insignificant.

Infants who were admitted with pneumonia were found to be at a higher risk (2.098 times) of death compared to their counterparts who were admitted without pneumonia.

A unit increase in age (in months) reduces the risk of mortality by 0.013 times.

Infants admitted with diarrhea were 0.624 times less likely to die than their counterparts who were admitted without diarrhea.

From table 3, the Weibull shape parameter was 1.5. This implies it is positively skewed and has a right tail in addition to a decreasing hazard of post-discharge mortality with time (as noted in the explanatory data analysis). The scale parameter was 1.58.

Table 3: *Parameter estimates, standard errors and p-values for the WFLz variable.*

Effect	Estimate	S.E	p-value
Intercept	-5.099	0.470	<0.0001
Treatment	-0.085	0.216	0.694
Pneumonia	0.741	0.272	0.0064
Diarrhea	-0.471	0.224	0.035
Age	-4.383	1.130	0.0001
Assoct	-0.034	0.027	0.2023
Log (shape)	0.462	0.109	<0.0001

4.5 MUAC results

The basic survival submodel containing only MUAC as a covariate was fitted. Likelihood ratio tests determined that two baseline covariates (site and treatment (p-value>0.05)) were not significant. Pneumonia (p-value=0.007), diarrhea (p-value=0.028) and age (p-value<0.001) were found to be significant. Site was dropped but treatment was retained in the model.

Numerical integration was done using adaptive Gauss-Hermite rule with 30 points. Convergence was concluded when the parameter estimates and the AIC values were no longer changing. Analysis was conducted assuming a Weibull baseline hazard for the survival submodel.

As shown in Table 4 the ‘Assoct’ parameter that measures the association between $M_i(t)$ (in this case the value of MUAC) and the risk ofdeathshows a significant relationship between MUAC and mortality (p-value=0.014). The parameter α quantifies the effect of the underlying longitudinal outcome to the risk for an event. A unit increase in MUAC (in centimeters) reduces the risk of death by 0.9 times.

Patients admitted with pneumonia were at a higher risk of post-discharge mortality (2.1 times) as compared to those admitted without pneumonia. Patients admitted with diarrhea were 0.6 times at a lower risk of post-discharge death as compared to those admitted without diarrhea.

Table 4: *Parameter estimates, standard errors and p-values for the MUAC variable.*

Effect	Estimate	S.E	p-value
Intercept	-4.290	0.530	<0.0001
Treatment	-0.087	0.216	0.6885
Pneumonia	0.740	0.271	0.0064
Diarrhea	-0.468	0.223	0.0361
Age	-4.395	1.127	0.0001
Assoct	-0.067	0.027	0.0143
Log (shape)	0.568	0.109	<0.0001

The Weibull shape parameter was 1.76. This implies it is positively skewed and has a right tail in addition to a decreasing hazard of post-discharge mortality with time. The scale parameter was 1.76.

CHAPTER 5: DISCUSSION

Joint models for longitudinal and time-to-event data have become a valuable tool in the analysis of follow-up data. These models are mainly applicable when the focus is on the survival outcome and we wish to account for the effect of an endogenous time-dependent covariate measured with error and when the focus is on the longitudinal outcome and we wish to correct for nonrandom dropout. Due to the capability of joint models to provide valid inferences in settings where simpler statistical tools fail to do so, and their wide range of applications, the last 25 years have seen many advances in the joint modeling field.

In this work the joint modelling approach proposed by Rizopoulos is presented. This methodology constitutes a useful tool to study the relationship between longitudinal and survival data. The joint modeling approach is used to determine if there is an association between the longitudinal measurements and the risk of mortality in a cohort of 1652 infants.

As shown in Tables 3 and 4 the 'Assoct' parameter that measures the association between $M_i(t)$ and the risk of death shows a significant relationship between MUAC and mortality (p-value=0.014). In contrast, WFLz was not significantly associated with mortality (p-value= 0.202). The parameter α quantifies the effect of the underlying longitudinal outcome to the risk for an event. A unit increase in MUAC (in centimeters) reduces the risk of death by 0.9 times. This finding concurs with that done by Mwangome et al (2012) in a retrospective study carried out using data from The Gambia that showed MUAC showed better performance than WFLz in identifying infants at increased risk of death. In addition joint modelling approach shows similar results with the sensitivity and specificity approach used in the research carried out in The Gambia.

The joint model of WFLz and mortality reported an AIC value of 27080.03 while that of MUAC and mortality reported an AIC value of 25025.79. When comparing these two models

to see which would be the better model, the one with the smaller AIC value is preferred. This means MUAC identifies infants at risk of mortality better than WFLz.

The major breakthrough of the joint models relative to the time-dependent Cox model, which is widely used to predict survival or failure, is that they allow one to deal with the error measurements in the time dependent variables (longitudinal variable in this case). In a Cox model with time dependent covariates we assume that the variables are measured without error. Given that joint modelling allows better capture of the information of the changing values of the longitudinal data over time, it would be expected that joint modelling would out-perform the Cox model especially in a situation when there is much error variation in the longitudinal values.

The strengths of this study include low drop outs due to a rigorous follow up system and hence low data missingness. Since this was a double blind and randomized study, there was no bias. The major advantage of joint modelling is that constantly provides better estimates of events of interest as compared to other traditional methods such as the Cox proportional hazards model, Özgür et al. (2015). Since joint modelling is still a relatively new technique, further development of corresponding statistical software is required. However, existing joint modelling packages have already demonstrated their potential usefulness and should be utilized to apply joint modelling in the analysis of relevant data.

The major limitation of this study was understanding the complex nature of joint modelling. Very little literature was available in some aspects of joint modelling since it is relatively new and hence not widely published. Joint modelling involves the simultaneous modelling of the two components, namely the time-to-event component and the longitudinal component. The major challenges of joint modelling are the mathematical and computational complexity. The main computational difficulty in joint modelling is that the integrals involved in likelihood

estimation are usually intractable in that they have no analytical solutions. So numerical approximations are usually required to evaluate these integrals.

CHAPTER 6: CONCLUSIONS AND RECOMENDATIONS

WFLz is still recommended for use by many organizations including WHO as an anthropometric standard of diagnosing malnutrition. The joint modelling results join a growing pool of research to show that MUAC would be a better standard to not only diagnose malnutrition but to identify infants at increased risk of mortality due to severe acute malnutrition. Even though it is recommended that MUAC should not be used as a stand-alone criterion of anthropometric diagnosis of acute malnutrition given its strong association with age, sex and stunting, and its low sensitivity to detect slim children, it consistently outperforms WFLz in its predictions. The mid upper arm circumference is a measure that is obtained more easily, quickly and more affordably as compared to WFLz. The mid upper arm circumference is currently not recommended for use among infants aged below 6 months because of a lack of data on its reliability.

Since joint modelling shows that WFLz is not strongly associated with post discharge mortality while MUAC shows a significant relationship with mortality, MUAC is taken to be the better predictor of post discharge mortality.

Joint modelling has given better predictive capabilities as compared to traditional methods and its application in analyzing data collected serially is recommended. It has also given consistent results it an anthropometric setting as compared to other approaches like sensitivity and specificity. Increased used of joint modelling is recommended when analyzing serial data.

In both cases involving MUAC and WFLz, children with diarrhea were observed to have a lower a lower risk of post-discharge death as compared to their counterparts without diarrhea. More research is recommended to better explain this finding.

REFERENCES

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control*, 19(6):716–723.

Berkley J, Ngari M, Thitiri J, *et al*. (2016) Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomized placebo-controlled trial. *Lancet Global Health*; published online June 2. http://dx.doi.org/10.1016/S2214-109X(16)30096-1

Berkley J, Mwangi I, Griffiths K, Ahmed I, Mithwani S, English M, (2005). Assessment of severe malnutrition among hospitalized children in rural Kenya: comparison of weight for height and mid upper arm circumference. *Journal of the American Medical Association*.;294:591–7.

Black R., Morris S., Bryce J. (2003). Where and why are 10 million children dying every year? *Lancet.* ;361(9376):2226-34.

Brewster, D. (2011). Inpatient management of severe malnutrition: time for a change in protocol and practice. *Annals of Tropical Pediatrics*; **31:** 97–107.

Bryce J, Boschi-Pinto C, Shibuya K, Black E.(2005) WHO estimates of the causes of death in children. *Lancet*. Mar 26-Apr 1;365(9465):1147-52

Chisti MJ, Graham SM, Duke T, Ahmed T, Faruque ASG, *et al*. (2014) Post-Discharge Mortality in Children with Severe Malnutrition and Pneumonia in Bangladesh. *PLoS ONE* 9(9): e107663. doi:10.1371/journal.pone.0107663

Faucett, C. and Thomas, D. (1996). Simultaneously modelling censored survival data and repeatedly measured covariates: A Gibbs sampling approach. *Statistics in Medicine* **15,** 1663 – 1685.

Fernandez MA, Delchevalerie P, Van Herp M.(2010) Accuracy of MUAC in the detection of severe wasting with the new WHO growth standards. *The Journal of Pediatrics*.;126:e195–201.

Fieuws, S., Verbeke, G., Maes, B., and Vanrenterghem, Y. (2008). Predicting renal graft failure using multivariate longitudinal profiles. *Biostatistics* **9,** 419 – 431.

Gebregziabher, M., Egede, L. E., Lynch, C. P., Echols, C. and Zhao, Y. (2010). Effectof trajectories of glycemic control on mortality in type 2 diabetes: a semiparametric joint modeling approach. *American Journal of Epidemiology*; 171:1090-8.

Guevarra E, Norris A, Guerrero S, Myatt M. (2012). Assessment of coverage of community based management of acute malnutrition. CMAM Forum Technical Brief One; Accessed 02 Oct. http://www.cmamforum.org/

Henderson, R., Diggle, P., and Dobson, A. (2000). Joint modelling of longitudinal measurements and event time data. *Biostatistics* **1,** 465 – 480.

Hsieh, F., Tseng, Y.-K., and Wang, J.-L. (2006). Joint modeling of survival and longitudinal data: likelihood approach revisited. *Biometrics* **62,** 1037 –1043.

Kerac M, Bunn J, Seal A, Thindwa M, Tomkins A, *et al*. (2009) Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomized trial in Malawi. *Lancet* 374: 143–144.

Lim, H. J., Mondal, P. and Skinner, S. (2013). Joint modeling of longitudinal and event time data: application to HIV study. *Journal of Medical Statistics and Informatics*; 1:1.

Lipsitz, S., Fitzmaurice, G., Ibrahim, J., Gelber, R., and Lipshultz, S. (2002). Parameter estimation in longitudinal studies with outcome-dependent follow-up. *Biometrics* **58,** 621 – 630.

Moisi J., Gatakaa H.. and Berkley J. (2011) Excess child mortality after discharge from hospital in Kilifi Kenya: a retrospective cohort analysis. *Bulletin of the World Health Organization*; 89:725-32, 32A

Murphy, T. E , Han, L., Allore, H. G., Peduzzi, P. N., Gill, T. M. and Lin, H. (2011).Treatment of death in the analysis of longitudinal studies of gerontological outcomes. Journals of Gerontology. *Series A, Biological Sciences and Medical Sciences*; 66:109-14.

Mwangome MK, Fegan G, Fulford T *et al*. (2012) Mid-upper arm circumference at age of routine infant vaccination to identify infants at elevated risk of death: a retrospective cohort study in the Gambia. *Bulletin of the World Health Organization;* 90, 887–894.

Mwangome M, Fegan G, Mbunya R, Prentice A, Berkley J.(2012). Reliability and accuracy of anthropometry performed by community health workers among infants under 6 month in rural Kenya. *Tropical Medicine and International Health*;17:622–9. doi:10.1111/j.1365 3156.2012.02959.x

Myatt, Mark, Duffield, Arabella, Seal, Andrew and Pasteur, Frances (2008)'The effect of body shape on weight-for-height and mid-upper arm circumference based case definitions of acute malnutrition in Ethiopian children', *Annals of Human Biology*,36:1.

Ngari M, Waithira N, Chilengi R, *et al* (2014). Experience of using an open source clinical trials data management software system in Kenya. BMC Research notes;7:845

Naomi, T.(2008). An investigation of anthropometric training by NGOs, , *Field Exchange Issue 32*,

Özgür A., James R., Philip A., Peter J. (2015) Joint modelling of repeated measurement and time-to-event data: an introductory tutorial. *International Journal of Epidemiology*; 44 (1): 334-344. doi: 10.1093/ije/dyu262

Proust-Lima, C. and Taylor, J. (2009). Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of post-treatment PSA: a joint modeling approach. *Biostatistics*; 10:535-49.

R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Rizopoulos, D. (2010). JM: An R Package for the Joint Modelling of Longitudinal and Time-to-Event Data. *Journal of Statistical Software*, 35(9), 1-33. URL http://www.jstatsoft.org/v35/i09/.

Rizopoulos, D. (2011) Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data. *Biometrics.*

Rizopoulos, D. (2012). Joint Models for Longitudinal and Time-to-Event Data. Boca Raton: Chapman and Hall/CRC.

Rizopoulos, D. (2011). Dynamic Predictions and Prospective Accuracy in Joint Models for Longitudinal and Time-to-Event Data. *Biometrics*, 67, 819âA¸S829.

Roberfroid, C. et al. (2015) Inconsistent diagnosis of acute malnutrition by weight-for-height and mid-upper arm circumference: contributors in 16 crosssectional surveys from South Sudan, the Philippines, Chad, and Bangladesh *Nutrition Journal* DOI 10.1186/s12937-015-0074-4

Self, S. and Pawitan, Y. (1992). Modeling a marker of disease progression and onset of disease. In Jewell, N., Dietz, K., and Farewell, V., editors, *AIDS Epidemiology: Methodological Issues*. Birkhauser, Boston.

Sweeting, M. and Thompson, S. (2011). Joint modelling of longitudinal and time-to-event data with application to predicting abdominal aortic aneurysm growth and rupture. *Biometrical Journal* **53,** 750 – 763.

Tsiatis, A. and Davidian, M. (2001). A semi parametric estimator for the proportional hazards model with longitudinal covariates measured with error. *Biometrika* **88,** 447 – 458.

Tsiatis, A. and Davidian, M. (2004). Joint modeling of longitudinal and time to-event data: An overview. *StatisticaSinica***14,** 809 – 834.

World Health Organization (1999). *Management of Severe Malnutrition: A Manual for Physicians and Other Senior Health Workers*. Geneva, Switzerland: World Health Organization;

World Health Organization (2000). *Management of severe malnutrition: a manual for physicians and other senior healthworkers.* Geneva: Available from: http://www.who.int/nutrition/publications/en/manage_severe_malnutrition_eng.pdf

World Health Organization (2015). Pocket book for hospital care of children: guidelines for the management of common illness with limited resources. 2005. http://www.who.int/maternal_child_adolescent/ documents/9241546700/en/ (accessed March 9, 2015).

World Health Organization (2009) child growth standards and the identification of severe acute malnutrition in infants and children A Joint Statement by the World Health Organization and the United Nations Children's Fund..

Wulfsohn, M. and Tsiatis, A. (1997). A joint model for survival and longitudinal data measured with error. *Biometrics* **53,** 330 – 339.

Ye, W., Lin, X., and Taylor, J. (2008). Semiparametric modeling of longitudinal measurements and time-to-event data – a two stage regression calibration approach. *Biometrics* **64,** 1238 – 1246.

Zhang, J. P., Kahana, B., Kahana, E., Hu, B. and Pozuelo, L. (2009). Joint modeling of longitudinal changes in depressive symptoms and mortality in a sample of community-dwelling elderly people. *Psychosomatic Medicine*; 71:704-14.