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UNIVERSITY OF MALAWI - COLLEGE OF MEDICINE RESEARCH and ETHICS COMMITTEE (KUHES REC) CHECKLIST TO ACCOMPANY NEW RESEARCH PROPOSALS SUBMITTED TO THE COMMITTEE

When you submit a research proposal for the Committee to approve, first read the document entitled ***KUHES REC Elements Of Review*** *attached to this check list. Make sure that your proposal is in the format outlined in the document.*

Before sending or giving the proposal to the Committee, complete the following check-list by ticking each item you have included. Do not submit the proposal *unless you can tick all the boxes, or provide a reason for the absence of any item. Attach the completed check-list to the front of your submission. Provide evidence of payment of US150 processing fee.*

TITLE OF PROPOSAL: Innovative Monitoring in PAediatrics in Low-resource settings: an Aid to save lives? (IMPALA)
Name of Principal Investigator: Jenala Njirammadzi & Job Calis
Name of Sponsor and amount of sponsorship: EDCTP 300.000 USD

Submit all documents in one pdf file of not more than 5MB by email to KUHES REC@medcol.mw (if the file size is more than 5MB, then please zip the file and submit it as a compressed zipped file).
The **single** pdf file should include the following information in the following order:

01	Completed copy of this checklist as stated above	Yes■or No☐
02	Covering letter of introduction from Investigator	Yes■or No☐
03	The study protocol which should include the following:-	
	Study Title	Yes■or No☐
	List of Investigators and institution(s) involved	Yes■or No☐

	Executive Summary		Yes■or No☐
	Background/Introduction		Yes■or No☐
	Rational/justification		Yes■or No☐
	Objectives of the study: Main objective and Specific Objectives		Yes■or No☐
	Methods:		
		Type of study - place of study	Yes■or No☐
		Study population	Yes■or No☐
		Study period Sample size	Yes■or No☐
		Data collection procedures	Yes■or No☐
		Data management/analysis	Yes■or No☐
		Presentation of results	Yes■or No☐
	Dissemination of results		Yes■or No☐
	Ethical considerations: including consenting procedures, participant compensation, participant confidentiality etc.		Yes■or No☐
	Possible constraints		Yes■or No☐
	Requirements		Yes■or No☐
	Training provided for study staff		Yes■or No☐
	Budget and Justification of budget		Yes■or No☐
	References		Yes■or No☐

04	Consent forms: include consent forms in both English & Chichewa for adult participants aged 18 and above, parental consent forms for all minors and assent forms (in addition to the parental consent forms) for all minors between the ages of 7 and 17 years. Any participant payments e.g. compensation, reimbursement etc should be stated by amount in the consent forms.	Yes■or No☐
05	Data collection tools (proformas): those that will involve obtaining information from research participants should be translated into Chichewa	Yes■or No☐
06	Material transfer agreement forms/documents	Yes■or No☐
07	Have you applied for a waiver of 10% COM overhead fee from the Office of Postgraduate Dean of Studies and Research? If yes, please attach a waiver letter.	Yes☐or No■
08	Have you submitted this proposal to another Ethics Committee? If yes, please specify whether approval has been given, and if approval has been awarded, please submit a copy of the approval letter with this submission	Yes☐or No■
09	Letter of support from COM Head of the Principal Department hosting the research	Yes■or No☐
10	Letter(s) of support from Heads of all other Depts. and institutions in which any research work will be done.	Yes■or No☐
11	Evidence of current active registration with the Medical Council of Malawi for Principal Investigator and other investigators who are involved in clinical research	Yes■or No☐
12	Brief CV of each investigator	Yes■or No☐

If any item is not ticked, explain why this is not included with the submission.

Signed: Name (print): Dr J Njirammadzi – Dr J Calis

Date: 07-02-2022

3.1 RESEARCH PROPOSAL FORMAT

[a] Title

Innovative Monitoring in PAediatrics in Low-resource settings: an Aid to save lives? (IMPALA)

In search of machine learning algorithms using vital signs and biomarkers to facilitate early life-saving interventions in paediatrics

[b] Investigators

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[c] Institution[s] under whose umbrella the research project will be conducted:

1. Kamuzu University of Health Sciences*
2. Department of Paediatrics and Child Health - Queen Elizabeth Central Hospital (QECH)
3. Zomba Central Hospital (ZCH), Department of Paediatrics
4. Training Research Unit of Excellence (TRUE)*
5. Malawi University of Business and Applied Sciences (MUBAS)*
6. Imperial College of London (ICL), United Kingdom*
7. Amsterdam Institute of Global Health and Development (AIGHD), (Amsterdam University Medical Center & Vrije University of Amsterdam) The Netherlands*
8. GOAL3, The Netherlands*
9. National E-Health Living Lab (NeLL), Leiden University Medical Center, The Netherlands*

***IMPALA Consortium members: KUHeS, TRUE, MUBAS, ICL, AIGHD, GOAL3, NeLL**

[d] Executive Summary

Type of Research:
An observational cohort study of 1000 children (28 days-60 months) admitted to the high dependency areas of Queen Elizabeth Central Hospital (QECH) and Zomba Central Hospital (ZCH).

The problem:
The number of children dying in African hospitals remains too high. A large part may be prevented if children can be observed more closely allowing timely life-saving treatments. Continuous monitoring of vital signs such as heart rate and oxygen saturation is applied for this reason in high-income countries but these techniques have not been adapted for low resource settings. New techniques of monitoring may make it possible to *predict* potential deterioration (and not just *detect*), these include new vital signs sensors, bedside blood tests (biomarkers) and artificial intelligence/machine learning.

The objectives:
The study aims to a) develop algorithms using vital signs to predict deterioration (critical illness) by applying a vital signs monitor developed for use in African hospitals; and b) test if biomarkers can help to predict critical illness alongside vital signs.

The methodology:
In this clinical observational study we will use the IMPALA monitoring system to gather the data required to develop the predictive algorithms that will be incorporated into a new version of the IMPALA system after this study. The data that will be collected will consist of vital signs (e.g. blood pressure, heart rate and respiratory rate) of 1,000 children admitted to the high dependency areas of two centres in Malawi (QECH and ZCH). Moreover, we will collect blood samples for bedside detection of biomarkers (RNA or protein) that may predict critical illness and sepsis. Additionally, anonymised sociodemographic data of the patients will be collected. These data and/or the biomarker data will optionally be used to strengthen the predictive power of the algorithms.

Expected findings:
The clinical-study firstly aims to construct several risk predictive models for both outcome and specific critical care actions using 1) continuously recorded vital signs alone and 2) including biomarkers and sociodemographic data. Secondly the clinical-study aims to define the accuracy of biomarkers predicting critical illness and bacterial sepsis.
The overall aim of the entire IMPALA project is to optimise monitoring of hospitalised children in low resource settings by integrating an algorithm that predicts critical illness events allowing early detection and treatment. The ultimate aim is to reduce amendable in-hospital deaths in children living in low-resource settings.

Dissemination:
The project will be part of three PhD programmes and its results will be shared through open-access peer-reviewed publications. Additionally, specific study results will be disseminated at the KUHeS Research Dissemination Conference, the involved departments and institutes in and to particular interest groups, both in meetings, workshops and conferences, nationally and internationally. All publications will be shared with KUHES REC. Additionally, the IMPALA

consortium and partners will disseminate the findings through their websites and media channels.

[e] Background information and introduction:

Relevance and scope

The major causes of mortality in children under the age of 5 are: diarrhoea, lower-respiratory tract infections (LRTIs), sepsis, malaria, TB and HIV.[1-4] Major advances in their management have been made in preventive and pre-hospital care strategies, however, the in-hospital mortality has lagged behind. Even in hospital settings, late recognition of critical illness is common and contributes to half of all in-hospital deaths, whilst early treatment can significantly reduce morbidity and mortality and is commonly available.[5-7] Critical illness is defined as the deterioration of vital systems, this includes severe problems with the airway, breathing or circulation, or acute deterioration of conscious state.[4-8] It is the combined final stage of these diseases and contributes significantly to their morbidity and mortality.

As the early detection or prediction of critical illness has a major impact on its prognosis, enabling early detection and treatment of critical illness through the development of a suitable vital signs monitoring system can significantly limit the impact of these diseases in low-resource settings (LRS) and especially sub-Saharan Africa (SSA). As an example, the in-hospital mortality in the High dependency units (HDU)/areas in Malawi is 12%. Halving the mortality in only the HDU could save the lives of an estimated 200 children per year in QECH, 2500 children in Malawi and 500,000-1,000,000 children globally.[9,10]

This innovation is particularly relevant in the present-day context:

- The recent advent of a next generation of high-quality, durable and cost-effective sensors and biomarkers strongly facilitates the development of an inexpensive paediatric vital signs monitoring system suitable for LRS.
- Novel machine-learning based methods have shown a demonstrable potential in prediction of critical illness and sepsis in high-resource settings (HRS), but this potential has not been realised in LRS yet.
- COVID-19 and other emerging and re-emerging infectious diseases are expected to continue to put a major strain on LRS health systems. Innovation which leads to more efficient use of scarce resources is especially relevant in this context.

Concepts underpinning IMPALA

Child mortality is concentrated in the youngest age groups, with 85% of all deaths in children under age of 15 years occurring among children younger than 5.[11] Reduction of preventable in-hospital paediatric mortality can be achieved by early recognition of critical illness, i.e. deterioration of vital systems, and provision of timely and appropriate interventions (e.g. patient review for respiratory support, fluid/blood supplements, antibiotics etc).[5,7] Early recognition of critical illness is enabled by monitoring of vital signs, which usually include heart rate, respiration rate, oxygen saturation and body temperature and more recently parameters such as heart rate variability and patient movement patterns.[12,13] Current monitoring systems however are not adequate for LRS as they often use expensive single use sensors; cannot record movement, convulsions and detect breathing poorly; and lastly are designed to detect rather than predict a critical illnesses which not only causes

many alarms and only facilitates late but not early (preventive) treatment.

1. Early detection or prediction of critical illness through monitoring of vital signs enables early treatment avoiding severe complications or death

In LRS, a large part of the mortality part may be prevented if children can be observed more closely allowing timely life-saving treatments.[14] Timely detection of patient deterioration is particularly challenging in LRS due to a lack of monitoring equipment and the low number of staff.[15,16] As a consequence, clinical monitoring often relies on ward attendants and parents/relatives who are less well-trained in recognition and reporting of critical illness causing a delay in response.

There are several key examples of how earlier intervention in hospitalised children vastly improves patient outcomes. For example in sepsis, diagnosing only 1 hour earlier results in >10% lower mortality.[7] Additionally, in malaria, severe complications can have a rapid onset in hours and are life-threatening unless adequate care is provided. In many patients, several of these complications exist together or evolve in rapid succession within a few hours.[17,18] However, symptoms for severe malaria with life-threatening complications include convulsions, respiratory distress and circulatory collapse, which are readily detectable through automated and continuous adequate vital sign monitoring.[12,13] Similarly, it has been established that for many other diseases the early identification and treatment can significantly limit mortality and morbidity.[7,19] Pneumonia, the leading cause of death among children younger than 5, can be monitored effectively as hypoxaemia is a good marker of disease severity and adverse outcomes.[20] This can be tracked with pulse oximetry and management of hypoxaemia with oxygen is associated reduced mortality.[21]

2. Improved monitoring systems lower the health & economic burden of childhood diseases.

Since scarce resources are available in SSA, including Malawi,[22,23] specifically designed vital sign monitoring systems that are easy to use, can enable professionals, support staff and even guardians to timely detect critical illness and potentially save thousands of lives. More importantly, accurate prediction of a high risk of critical illness will enable doctors to prioritise care more efficiently and reserve the use of the scarcely available high-intensity care for those patients who have the highest risks of morbidity. Early treatment and avoiding serious morbidity enabled by reliable vital signs monitoring will lead to less use of expensive care, shorter hospitalisation, faster recovery and thus also reduce economic burden of childhood diseases.

3. Through a new generation of technologies in sensors and machine learning, monitoring systems can be improved to become predictive, precise and cost-effective

Adequate vital sign monitoring to timely detect and algorithms to predict clinical deterioration can, especially in LRS, be life-saving and strongly limit the economic burden of health and childhood diseases. Unfortunately, very few initiatives have seen widespread implementation in LRS,[4] because they are designed for HRS and lack specific features needed for adoption in LRS, such as low-cost, robustness, low-maintenance, and ease of use. Moreover, current affordable monitoring systems too often still lead to inaccurate and limited measurements or are highly-labour intensive for already overwhelmed staff as they are not automated.

Our overall goal is to improve a monitoring system for use in LRS by integrating critical illness predicting algorithms, being sustainable, affordable, and easy to use so that health workers can

provide timely and effective care to the right patient at the right time.

Trends in monitoring and diagnostics

Recently, there has been an exponential growth in potential and cost-effectiveness of smart sensors due to intensive research in this field which has moved at an incredible pace. As a result, the market for medical sensors has grown tremendously and is predicted to keep growing.[24,25] The growth in reliability and durability of affordable sensors has made it more feasible now than ever to develop cost-effective systems for LRS.

This has been paired with advances in vital signs monitoring that will allow us to simplify, improve and adjust vital sign monitoring devices for use in LRS. Examples of these advances include the discovery and recognition of new vital signs,[26] new analytical techniques using machine learning (see below) and new technologies such as ballistography, mobile point of care (POC) lab tests, wireless communication methods, mobile technologies, battery operated equipment and reusable sensors.[12,13]

In the IMPALA project, we propose to leverage the recent advancements in sensors, biomarkers and machine learning to improve the IMPALA-system specifically for use in LRS and co-developed with end-users and stakeholders. To achieve this we have identified the following new technologies.

1. Sensor technologies

Ballistography is a method that allows continuous monitoring of movement, respiration- and heart rate using a reusable, robust and easily cleanable thin foil placed underneath the cover of the mattress of the patient and does not need to be discarded after use; which is thus especially suitable for LRS. This technology has great potential for improved monitoring of respiration rate, which is the most accurate predictor of developing critical illness.[27] GOAL 3 has developed a cost-effective prototype vital signs monitor for LRS (IMPALA 1.0) based on a ballistographic sensor in addition to traditional sensors like pulse oximetry, non-invase Blood Pressure and ECG. The sensor and set-up was extensively tested in the Netherlands and the previous pilot project in Malawi showed promising results (KUHES REC 2945). For this study a model improved using the pilot study results will be used (IMPALA 2.0).

2. New vital signs

Heart rate variability, breathing rate variability and alterations in movement are new vital signs that allowed us to detect critical illness at an even earlier stage in a recent study in a paediatric hospital in the Netherlands. Here we showed it may be possible to detect critical illness and sepsis in neonates up to six hours earlier than clinicians.[12,13] This pattern was also identified in patients in a pilot study with the IMPALA monitor in Malawi (KUHES REC 2945). We hypothesise that the potential time gained to diagnose a critical illness may be even higher if the human and other resources to detect deterioration are limited.

Although these results are promising, the predictive value of these parameters to detect critical illness needs to be evaluated in large African datasets. Further analysis is also required on how to process these signs so they can be easily interpreted by clinicians. Combining these new vital signs

with existing parameters in algorithms could further improve the accuracy to detect and predict critical illness at an early stage and these composite scores would be easily interpretable for clinicians.

3. Big data and machine learning

The use of big data and machine learning algorithms in critical care have the potential to facilitate the prediction of critical deterioration and yield significant increases in cost-effectivity and management of resources in paediatric care.[28,29] For example, in 2014 a logistic regression algorithm based on various vital signs such as respiratory rate, heart rate, oxygen saturation and blood pressure already outperformed two widely employed Paediatric early warning scores in predicting the need of paediatric intensive care unit transfer for newly hospitalised children.[30] Machine learning models and conventional statistics have been used extensively in HRS for predicting clinical deterioration and outcomes based on vital signs and laboratory values with considerable success.[31-33] Our consortium has had similar successful experience in developing machine learning algorithms for the prediction of morbidity and mortality.[34,35]

Nonetheless, very few studies have attempted to apply these methods to LRS. A notable exception is the study performed by Imperial College London (ICL) who have successfully demonstrated the potential and feasibility of predicting clinical deterioration in LRS paediatrics. Based on data derived from a previous study in 3,170 severely ill children (the FEAST trial), they were able to develop a clinical bedside risk score to identify those children at greatest risk of mortality based on a set of 8 vital signs supplemented with several easily measurable biomarkers.[36] The score discriminated those at highest risk of fatal outcome at the point of hospital admission and compared well to other published risk scores. By leveraging the unrivalled potential of novel machine learning technologies, we will incorporate the ability to even predict critical illness and vital signs deterioration in children. If this can be achieved it is expected to decrease both morbidity and mortality.

4. Blood-based biomarkers

In addition to commonly used predictors such as serum lactate and C-reactive protein (CRP), several new biomarkers for critical illness and bacterial sepsis are being discovered. The blood-based biomarkers that were identified by ICL as prognostic factors for critical illness can be measured through simple laboratory tests to complement the analysis of the continuous vital sign monitoring. RNA expression profiling to identify highly expressed genes predictive of poor outcome, proteomic analysis to identify protein biomarkers of poor outcome. In initial analysis of RNA expression data from over 3,000 patients included in the PERFORM study we have identified a small number of highly expressed RNA transcripts or proteins which predict poor outcome, including RNA transcription markers (FAM89A and IFI44L) and protein biomarkers.[37] ICL is currently involved in a long-term research trajectory to enable the sustainable availability of these biomarkers in LRS as part of the DIAMONDS and FEAST studies. A recent report provides proof of principle using a handheld microchip based platform that enables detection of the predictive signatures at low cost.[38] As a key step in this trajectory, the predictive value of intermittent measurement of biomarkers will be validated in the IMPALA project and it will be investigated if they can supplement the predictive strength of the predictive IMPALA algorithms.

In the IMPALA project, we will synergistically combine the potential of machine learning in paediatric critical care with our patient monitoring device based on innovative ballistography. We will venture into largely uncharted waters and specifically design algorithms based on LRS data of vital signs optionally supplemented with easily measurable blood-based biomarkers and clinical and demographic data.

After this study we plan to integrate these algorithms into the IMPALA-system (IMPALA 3.0), enabling the early prediction of critical illness in children in LRS, which will facilitate early detection and treatment. For this study we will separately apply for ethical clearance in the future.

[f] Rationale/justification for the research project:

We recently reported that it is possible to detect changes in vital signs through machine learning algorithms up to six hours before a sepsis diagnosis is suspected in European neonates.[10,11] The ability to detect sepsis hours earlier and start antibiotics may have a huge impact, as mortality in sepsis increases by 10% for every hour left untreated.[7] Like sepsis there are several other critical care treatments such as respiratory support, intravenous fluid and blood products, inotropes, anticonvulsants and emergency surgical procedures, that can reduce morbidity and mortality if given **early** in the course of disease.[5] Early treatment was also shown to be cost-effective in LRS.[39]

To enable early detection of critical illness, vital signs monitoring is commonly used in high income settings. Modern techniques including new vital signs, novel biomarkers and algorithms combining these data using machine learning, a powerful technique that can analyse trends in vital signs using algorithms, can be used to detect these critical illnesses even earlier.[28-33] In settings with limited (human) resources these techniques and algorithms may prove even more valuable as they may help to signal deterioration hours earlier than human detection. Early detection would enable earlier treatment, potentially reducing morbidity and mortality in hospitalised children. No algorithms currently exist however for Malawi or other paediatric populations in low-resource settings. These algorithms may be very different from high income settings, a lesson we learned from developing conventional vital sign prediction models (CISSAC project - KUHES REC #2557 M. Kumwenda/R. Assiess, submitted for publication).

In this observational study we aim to closely monitor a population of hospitalised children in Malawi with a high risk of developing critical illness. The primary aim is to develop algorithms to predict critical illness using vital signs collected using a vital signs monitor improved for and successfully piloted in Malawi (IMPALA 1.0, KUHES REC #2945). In addition to vital signs, we will assess the use of novel biomarkers and sociodemographic data to predict critical illness. The results from this study and the identified algorithms will be integrated into an updated version of our IMPALA monitor (3.0). This may help to predict critical illness facilitating early interventions potentially reducing mortality of hospitalised children in Malawi and beyond.

[g] Objectives of the study

[i] Broad (Primary Outcome)

To predict critical illness in Malawian children using vital signs monitoring and applying machine learning to detect, train and test a predictive algorithm.

[ii] Specific (Secondary endpoints)

1. To assess the contribution of adding sociodemographic data to the predictive power of the algorithms.

2. To assess the potential added role of a predefined set of biomarkers in a predictive algorithm to detect critical illness. These markers will be including POC testing of lactate, two RNA transcription markers (FAM89A and IFI44L), C-Reactive protein and further analysis including previously described and novel markers now and in future.[7]

3. Design separate predictive models for critical illness in a better-resourced centre (Blantyre) as compared to a less-resourced centre (Zomba) which may more closely resemble most sub-Saharan hospital settings and assess the accuracy of these models.

4. Design separate predictive models for critical illness in infants (aged between 28 days and 12 months) and older children (12 to 60 months) and assess the accuracy of these models.

5. Make predictive models using conventional statistical approaches to compare the accuracy (sensitivity, specificity, false-positive and negative ratios, and area under the curve) of our model(s) against models published in literature or identified in a retrospective dataset.

Monitoring data will further be used to improve sensor selection, software and hardware of the monitoring device. As part of this project, but not this study, we will perform other studies assessing important elements concerning the health economics, usability and social science aspects. These have been recently submitted to KUHES REC (#3552).

[h] Methodology

i] The type of research study

Type of study, study phase and classification

This is a clinical observational study aimed at identification of predictors of critical illness events in children using vital signs, clinical information, and biomarkers. The aim is to develop an algorithm to predict critical illness with vital signs alone and with a combination of vital signs, clinical information and/or biomarkers combined. Machine learning will be applied to identify (train) and validate (test) the model using several cross-validating techniques.

The study will admit a cohort of 1,000 children (aged between 28 days and 60 months) admitted to high dependency areas. The IMPALA vital signs monitor (prototype 2.0) will continuously record vital signs during admission to these areas. Vital signs will include heart rate and heart rate variability, respiratory rate, movement, oxygen saturation and non-invasive blood pressure. In addition, we will collect a venous blood sample and a nasal swab upon recruitment to assess conventional pathogens (malaria, blood culture and viral respiratory PCR) alongside RNA-transcription and protein biomarkers for critical illness in general and bacterial sepsis.[7]

Protecting against source bias

To prevent selection bias, we will recruit at any time of day/night. In addition decisions to admit or discharge children to the high dependency areas, as well as all therapeutic and diagnostic decisions, will only be made by hospital staff, following hospital protocols.

Interventions and standard care

After connection of the monitor observation of routine clinical practice is the main aim of the study. After informed consent, an electronic case record form (e-CRF) will be completed containing sociodemographic data, previous and current medical history, and a physical examination will be performed including collection of anthropometric data (Annex 1b-d).

We will collect a nasal swab for viral PCR testing, a urine sample using a bag for dipstick detection of urinary tract infections and a blood sample will for pathogen detection (blood culture and malaria slide) and biomarker testing (POC lactate, and delayed testing of CRP and other biomarkers). All tests will be run at KUHeS. If additional consent is given these samples will be stored and used for later evaluation of new biomarkers and biomarkers discovery programmes at KUHeS or in the United Kingdom.

All children participating in the study will be attached to the IMPALA 2.0 monitor, which will consist of the BCG-sensor, a saturation probe placed on a finger, toe or hand, three ECG electrodes placed on the chest and a blood pressure cuff around the arm or leg. The monitoring will be in addition to current hospital monitoring practises, which differ per ward. For children admitted to the new HDU in QECH this will be in addition to the currently used continuous monitoring system. In the other high dependency areas in the study monitoring is done using intermittent monitoring

checks by the hospital staff, which will also continue during the study. Monitor readings will be displayed during the study and alarms will have high thresholds (Saturation<85%; heart rate <60/min or >220/min) to prevent too frequent alarms.

During the study children will receive routine care provided by the hospital staff according to hospital protocols. The study team will be present 24/7 to record if critical illness or other events occur.

Critical Illness

The definition of critical illness is based on the WHO ETAT (paediatric Emergency and Triage assessment and treatment) updated Manual.[5] Critical illness is defined as a severe problem with the airway, breathing or circulation, or acute deterioration of conscious state.

Since the algorithm will be aimed at predicting deterioration to allow interventions, the chosen endpoints or *critical illness events* are primarily therapies aimed at preventing deterioration or restoring the normal function of these systems. (P)ICU admission and death were further added as these are commonly accepted endpoints in prediction models.

Critical Illness Events (Primary outcome)

Respiratory	- Start or increase of respiratory support: oxygen or CPAP
	- (Non)Invasive ventilation: bag & mask ventilation or intubation
	- Start or increase of bronchodilator support
Circulatory	- Transfusion of blood (products)
	- Intravenous fluid bolus of 10ml/kg or more
	- Start or increase of continuous/intermittent inotropic support (IV/IM adrenalin)
	- Cardio-pulmonary resuscitation (CPR): resuscitation setting involving chest compressions
Neurological	- Decrease in Blantyre Coma Score of 1 point or more
	- Convulsions requiring anticonvulsants
Other	- Sepsis: clinical suspicion of sepsis that has led to the collection of a new blood culture and/or start or change in antibiotic treatment[2]
	- Start of anti-malarial treatment
	- Objectified hypoglycaemia requiring correction (IV or enteral)
	- Unplanned admission to the (P)ICU
	- Unplanned surgical procedure (including chest drains)
	- Death

Other parameters collected

- Clinical diagnosis on admission and discharge
- Medical and surgical interventions (including medication)
- Clinical observations during admission (including manual vital signs)
- IMPALA vital signs monitor alarm logs and system data
- Haematological, biochemical, radiological, and microbiological results
- Overall outcome and duration of hospital admission

ii] Study Place

The study will be performed in two hospitals in Malawi: Blantyre – Queen Elizabeth Central Hospital and Zomba – Zomba Central Hospital. Both settings will be compared in our cross-validation assays (geographical validation).

Blantyre

Queen Elizabeth Central Hospital Blantyre is a tertiary referral and academic hospital. The paediatric department has approximately 15,000 admissions per year and has specialised wards including neonatology, oncology, malnutrition, paediatric surgery and paediatric intensive care. Most patients are admitted to the paediatric nursery (infants less than 6 months old) and the paediatric special care ward (6 months old and above). Within these wards, separate bays, called high dependency bays, are reserved for patients requiring more intensive supervision or treatments. These high dependency bays can admit 14-30 patients in the paediatric special care ward and 19-24 in the paediatric nursery, and together admit approximately 2700 children per year. The overall mortality in the paediatric special care ward is 3.1% and in paediatric nursery 4.0%, most children dying in the high dependency bays.[33] The overall mortality in high dependency bays is 10% (range 8.2-13.6%). More recently a 15-bed high dependency unit was opened.

Zomba

Zomba Central Hospital is a large hospital with over 6000 paediatric admissions (data from 2019), excluding neonatology. The overall mortality among paediatric patients was 3.7% (hospital data management). Like Blantyre the sickest patients are admitted to the high dependency bays, admitting approximately 1200 patients per year. The paediatric unit is mostly run by clinical officers and a paediatric consultant. There is a general ICU ward that may occasionally admit a child (in 2019, 16 children were admitted) and the number of other specialists is limited.

Selection of sites

The study sites were selected as both have a large number of patients and have well-established research facilities. Zomba was more recently involved in research but is home to the TRUE research institute. Zomba was chosen as the facilities and the setup is more like most African hospitals.

iii] Study Population

IMPALA is aimed at early prediction of critical illness in hospitalised Malawian children to facilitate the early application of potentially life-saving therapies. The main focus will be on a population of children with a high chance of deterioration and a high mortality.

Inclusion & rationale

- Children aged 28 days – 60 months that will be admitted to the high dependency areas

The aim is to recruit children aged 28 days – 60 months that are admitted to the high dependency areas of the paediatric wards in Zomba (n=1) and Blantyre (n=3: the new HDU and the high dependency bays of paediatric special care ward and paeds nursery). There are no strict admission criteria for placing a child in the high dependency beds in either hospital, however the new HDU in QECH has admission guidelines. In practice children will be admitted to these beds if they have a high chance of developing critical illness as judged by the medical team, require more nursing care, or need specific treatments that are only available in HDU. These include oxygen therapy, nebulisation, CPAP, chest drains, blood transfusion, continuous infusions and inotropic support.

We chose to recruit in the high dependency bays as these children have the highest likelihood of developing critical illness; furthermore, this group may be the most likely population on which the monitoring system will be applied in future. We chose to recruit young children because this is the population with the highest mortality, clinical deterioration is less obvious than in other age groups and disease progression may develop more rapidly than in older children.[5-10]

Exclusion & rationale

- Children outside the age range
- Children not admitted to the high dependency bays/ward
- Children in whom monitoring is technically not possible
- No informed consent was given on admission

We will exclude children in the first four weeks of life and children admitted to the neonatal wards to exclude specific pathologies associated with prematurity, transition, birth trauma and early onset neonatal sepsis.[10] We will further exclude children when it is not technically possible to record vital signs (such as children with extensive burns on the chest region where ECG electrodes are placed) and those whose guardians that refuse or cannot give informed consent within the first 24 hours of high dependency admission.

Subgroups

The study will assess two main subgroups.

Firstly, two study sites in Malawi have been selected that have different resources: Queen Elizabeth Central Hospital Blantyre and Zomba Central Hospital. The first site is a tertiary referral and academic hospital with a higher number of medical staff including registrars, paediatric consultants

and nurses. There are more diagnostic and curative facilities, including a paediatric intensive care unit, and the presence of other medical specialties. Zomba Central Hospital is a large hospital with a high number of (paediatric) admissions. The paediatric unit is run by clinical officers and a paediatric consultant. There is a general ICU ward that may occasionally admit a child and the number of other specialists is limited. Both settings will be compared in our cross-validation assays (geographical validation).

Secondly, we will compare two different age groups: infants aged under 12 months and pre-school children (12-60 months). This stratification will be done as the physiology of vital signs, clinical diagnosis and main paediatric wards to which children are admitted are different.

Lastly, we will specifically study children with specific critical illnesses including the clinical diagnosis (bacterial) sepsis.

iv] Study Period

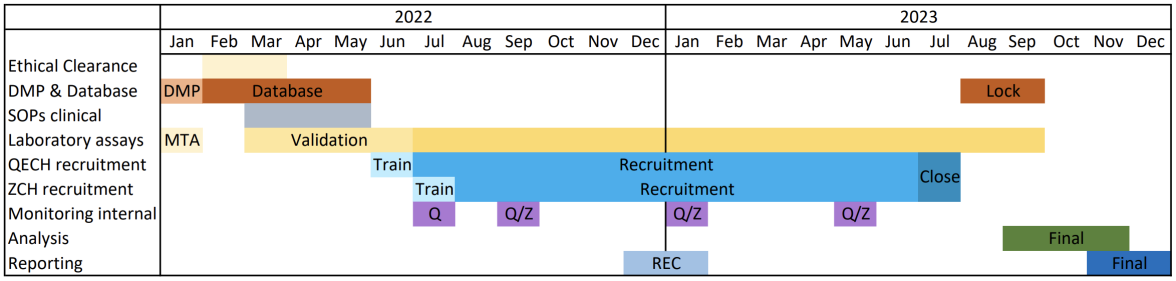

Figure 1. Gantt chart of the study activities

Preparation

During the preparation of the study several elements will take place according to **Figure 1**. Key documents are written including a Data management plan, Material and data transfers agreements, SOPs, validation of the laboratory work and recruitment and training of the study teams in GCP, obtaining informed consent, safety and relevant technical, sampling and clinical tasks involved in the project.

Recruitment

The first patient recruitment will start in QECH in July 2022 and ZCH in August. This will allow time to monitor the quality by the PI´s at study start and this will continue at regular intervals both for quantity (monthly) and quality (**Figure 1**). In both sites last patient enrolment will be June 30th and the last patient discharge will be July 2023 leading to a study close-out. Laboratory work will be performed throughout the recruitment phase in batches and the last initial retrospective testing is expected to end in September 2023.

Analysis

The final database lock for the clinical study will take place in August 2023 (clinical data) and September 2023 (laboratory data). The final study analysis will take place September-November 2023. The final study report is planned for December 2023.

v] Sample Size

General note & overall sample size

The main aim of the study is to design algorithms to detect critical illness in Malawian children using modern techniques. We aim to recruit 1,000 children who will render approximately 4-6,000,000 data points for each vital sign recorded. The primary analysis of this big dataset will therefore be based on machine learning techniques to detect and validate our model. In parallel, we will carry out a conventional statistical analysis. In our study design we have selected two different study sites to allow several methods of cross-validation including geographical validation. In designing the clinical observational studies and establishing sample sizes, the IMPALA consortium includes experts in statistics, data science and machine learning.

Sample size

The sample size of 1000 children was based on a) an estimate of an adequately large database to perform machine learning for model training, testing, and cross-validation; b) allowing conventional logistic regression analysis strategies.

Based on historical data of children in the high dependency units (HDU) in QECH and data from our pilot study, the estimated incidence of critical illness during the study time period is at least 10-15% and mortality in the HDU is 8-12%. Based on these low rates we expect 100-150 events (cases of critical illness). We will assume that for every 10 events one co-variate can be entered in the model, which is a generally accepted rule of thumb. As we expect that a model including 5 variables should provide sufficient predictive power, the anticipated 100-150 events in a sample size of 1,000 children is reasonable. In the case that the analysis would be stratified, for example according to location (QECH or Zomba Central Hospital) or age (less than 12 months or 12-60 months), the estimated number of patients in each group is estimated to be 500, still allowing at least 5 variables in the statistical model.

Given the set-up of an in-hospital study with close, 24-hour monitoring and critically ill patients the chance of loss to follow-up is limited. The major anticipated reasons for loss to follow-up in this setting may be absconding (<1% in Blantyre), or withdrawal of consent during the study. We will continue recruitment until 1000 have completed the monitoring and are discharged to the main bays.

vi] Data Collection:

A. Recruitment

Recruitment at each site will follow the same basic scheme. Patients who will be referred to the high dependency bays by the hospital team, based on their clinical judgement, will be approached by the study nurse that will be present 24/7. If the patient is eligible according to the recruitment criteria, counselling of the parents or guardians will be done according to GCP standards by a trained and certified nurse. If written informed consent is given, the vital signs monitor will be attached, an e-CRF completed (Annex 1b) and a urine sample, blood sample and nasal swab will be collected. Patients will be followed during their admission to the high dependency bay and monitored until discharge from this bay (Annex 1c). The study nurse will actively screen for critical illness and other clinical events and collect additional outcomes on discharge from HDU and hospital (Annex 1d).

Both KUHeS and TRUE (Zomba) have extensive experience with large patient studies. Blantyre has additional extensive experience in research concerning critically ill children. As this type of research is relatively new to the paediatric wards of Zomba Central Hospital, the Zomba study team will be trained in Blantyre first and recruitment will start 4 weeks later in Zomba.

In Blantyre and Zomba on average 7.4 and 3.3 patients are admitted daily to the high dependency areas respectively. We aim to recruit a minimum of 2 patients per day per site during the study period. During a 9-month period we could recruit the target of 1,000 patients, however teams will be able to recruit up to 12 months if enrolment is lower than anticipated.

Given the in-hospital observational design of this study we expect minimal loss to follow-up. In general, less than 1% of paediatric hospital admissions abscond (departmental data QECH) and in a similar study we did not have any loss to follow-up during admission in 377 critically ill patients.[40]

B. Monitoring - continuous and intermittent

During admission we will collect both *continuous vital signs* using the IMPALA 2.0 monitor and reusable sensors and *intermittent vital sign*s that can only be collected manually.

Continuous vital signs - sensors

After consent we will attach the IMPALA 2.0 monitor by:

- Attaching a pulse-oximetric sensor to the finger/toe of the child (**table 1**)
- Attaching three ECG electrodes to the chest
- Attaching a non-invasive blood pressure sensor to the arm or leg if appropriate
- Placing the child on a ballistographic sensor which will below the mattress

The commercially available sensors are validated and tested for use (**table 1**).

Sensor	Measures	Validated
Pulse oximeter	Oxygen saturation Pulse rate	Certified according to the related 60601 standard and each system as will be used under the study is tested by GOAL3 with an appropriate and calibrated Fluke* tool
Electrocardiogram	Heart rate Respiration rate	Certified according to the related 60601 standard and each system as will be used under the study is tested by GOAL3 with an appropriate and calibrated Fluke* tool
Non-invasive blood pressure sensor	Systolic pressure Diabolic pressure Mean pressure	Certified according to the related 60601 standard and each system as will be used under the study is tested by GOAL3 with an appropriate and calibrated Fluke* tool
Ballistography sensor	Respiration rate Heart rate Movement	With data from Pilot study 1. Output will only be displayed after validation within study.

Table 1. describes the different sensors that are being used. *The Fluke Prosim 8 is the golden standard for testing the different sensors.

Continuous vital signs - monitor

The IMPALA system is designed by the social enterprise GOAL3 in collaboration with MUBAS and consists of three components:

- The patient monitoring system that measures the vital signs. The hardware of the system is based on an existing commercial patient monitor developed by Witleaf (Witleaf Medical Electronics Co, ShenZhen) that is adjusted to integrate the ballistography (BSG) sensor. The monitor is tested according to the 60601 medical device safety standards.
- A small data storage server to which all the monitors are connected will be placed in the nursing stations.
- Tablets with an application will provide an overview of live data of all local monitoring systems connected to that server that can be placed in the nursing station.

The tablet and server are password protected. Data will be stored under the study and/or monitor numbers. A back-up of the server will be made regularly by the study team as the server will not be connected to the internet. The connections are password protected.

Intermittent vital signs

In addition to the continuous monitoring, nurses will gather routine 6 daily vital signs including temperature, Blantyre Coma Score, capillary refill time, pulses, limb temperature and pallor as well as clinical observations (Annex 1c). A daily weight will be taken. As most of these data are routinely collected for clinical purposes we will enter these on the e-CRF and the hospital charts to minimise the impact for the patients.

C. Laboratory Assays

The laboratory assays in this study will have two aims:

- assess the use of biomarkers to predict critical illness events in general
- assess the use of a biomarkers to detect bacterial sepsis and distinguish it from viral or parasitic infections

Sample collection

Study samples will be collected on study enrolment after informed consent. A repeat sample will be collected in children with the critical illness event *sepsis.*

<u>On enrolment</u> (admission to the high dependency area) we will collect:

- 1-2 ml for blood culture and malaria microscopy (if not yet collected in the prior 24 hrs)
- 1-2 ml venous blood sample in a EDTA tube for biomarker testing and storage
- A nasal swab for detection of respiratory viruses using PCR
- 2-10 ml urine using a urine collection bag for dipstick testing and storage

<u>New septic episode</u>

If during the study the clinical team decides to collect a new blood culture and/or start or change antibiotics, the study nurse will ask the clinical team to draw an additional 2 ml for:

- 1-2 ml venous blood sample in a EDTA tube for biomarker testing and storage
- malaria microscopy (if not yet ordered by the clinical team)

The study nurse will further collect

- a new nasal swab for detection of respiratory viruses using PCR
- 2-10 ml urine using a urine collection bag for dipstick testing and storage

Children will not be pricked extra for these samples. All the above samples will only be collected if we can combine collection sampling with that of the clinical team.

Sample processing

The ***PCV, Malaria microscopy and blood cultures*** will be performed by the main laboratory in ZCH, Zomba and the Wellcome trust research laboratories in Blantyre. Both Laboratories make use of an automated system for blood cultures.[41]

The ***Nasopharyngeal swab*** will be placed into 1.5mL UTM transportation media and stored in a -80C freezer. After thawing them in batches Nucleid Acid will be extracted using a commercial kit (e.g. MagNA Pure, Roche). We next will perform a multiplex platform aimed at influenza viruses (A and B), enterovirus, adenovirus, respiratory syncytial virus (A and B), rhinovirus (A-C), human metapneumovirus; parainfluenza viruses (1–4), parechovirus, human bocavirus and coronaviruses (including SARS-CoV-2). With every extraction and PCR, three controls will be run.[42] These storage extraction and PCR will be performed in KUHeS.

The 1-2 ml EDTA sample will be used to evaluate the accuracy of biomarkers to a) **predict**

critical illness events or b) **diagnosing bacterial sepsis** and differentiate bacterial, viral and parasitic infections.

Predicting critical illness events

- **Lactate** will be measured bedside using the Accutrend plus bedside test (Roche, Switzerland). Lactate is a commonly used predictor of outcome and was recently also found to predict outcome in the paediatric intensive care unit in Malawi (M. de Visser, submitted).[21]
- A protein predictive biomarkers (**Angiopoietin-2**) will be assessed using Immunoassay or RT-PCR in KUHeS.[43] This marker has been previously associated with critical illness/poor outcome and could be used for the development of the predictive algorithm.[43]
- During the course of the IMPALA study additional biomarkers are expected to be identified as part of the DIAMONDS study that is being performed by the Imperial College London- members of the IMPALA cohort (***Rec no. 20/HRA/1714***). The predictive accuracy of these markers in the IMPALA cohort will be evaluated on the stored samples in KUHeS using Immunoassay and RT-PCR techniques.

Diagnosing pathogens

- **C-reactive protein (CRP)** will be measured using a commercial Immunoassay at KUHeS. CRP is a commonly used predictor to distinguish bacterial from viral infections.[40]
- Second aim is to evaluate the discriminative ability of two new biomarkers **(FAM89A and IFI447**) to detect and differentiate between bacterial, viral and parasitic infections. The analysis will be done using Immunoassay, RT-PCR and/or RT-LAMP techniques in KUHeS.[37,38]
- During the course of the IMPALA study additional biomarkers are expected to be identified as part of the DIAMONDS study that is being performed by the ICL-team. The diagnostic accuracy of these markers in the IMPALA cohort will be evaluated on the stored samples in KUHeS using Immunoassay, RT-PCR and RT-eLAMP techniques.[37,38]

Additional information on novel biomarkers discovery and biobanking

There is an urgent need for improved diagnostics for use in African countries. The IMPALA cohort can be used to, not only evaluate currently identified biomarkers of disease severity and to diagnose pathogens, but can be used for discovery of new biomarkers appropriate for use in African countries.

Impala will attempt to undertake all laboratory studies for testing existing biomarkers and devices by RT-PCR, and Immunoassay, which are established methods in Malawi. However discovery of new biomarkers specific for African settings using RNA sequencing, and proteomic methods will require samples to be shipped to the UK or Netherlands, and determined by international providers of these methods.

Impala will benefit from collaboration with other EU funded biomarker studies, such as the DIAMONDS consortium, and techniques for pathogen detection using metagenomic sequencing. Diagnostic methods, not available in Malawi or funded on Impala may be offered in Collaboration with DIAMONDS but will require aliquots of blood or urine or nasal swabs to be sent to the UK.

vii] Data Management and Analysis

Data management

The data from both study sites will be entered on a password-protected tablet using an e-CRF (Annex 1b-d) using redcap and stored into an anonymised database by our study team. Both locations will have access to secure local servers to store their data. The central database will be located at Zomba Central Hospital, specifically at the Training and Research Unit of Excellence (TRUE). In some cases, data will be directly stored in the central database (i.e., data recorded in the eCRF or data generated in Zomba Central Hospital). In other cases, and where it is not immediately possible to store the data in the TRUE central server, data will be first stored locally and will be transferred to TRUE via secure cloud transfer (i.e., monitoring data and non-clinical data from implementation research). Access to consortium researchers will be arranged specifically according to their roles. This process is extensively described in our DMP.

Data analysis

We aim to develop algorithms to predict critical illness with vital signs alone and with a combination of vital signs, clinical information and/or biomarkers. The primary analysis of this big dataset will be based on machine learning techniques to detect and validate our model as these are more powerful and can manage the enormous amount of data(points) that continuous monitoring will generate. In parallel, we will carry out a conventional statistical analysis.

Machine learning approach

To develop robust machine learning-driven models that can recognise and predict critical illness based on the data collected using the novel monitor combined with other relevant patient data is challenging. This is for two reasons: (1) the type of data (time-series data combined with static patient characteristics), and (2) the high number of patients and vital signs that are available in the dataset. In the end, the goal is to deliver machine learning models that can be applied to a broad group of patients and generalise well to all settings where we envision applying the novel approach. To address these challenges, we will exploit a variety of state-of-the-art machine learning solutions.

Type of data: time series and static patient characteristics

To analyse temporal sensory data, feature engineering or using temporal machine learning algorithms are commonly used[44] and will both be applied in this project. Feature engineering approaches create features that summarise the sensory signal over time. Such features can act as input to well-known machine learning approaches such as XGBoost,[45] Random Forest,[46] Decision trees[47] or logistic regression. These models have the advantage that they can usually be easily understood. There is however inherently a bias in the design of such features.

Alternatively, we will also study the use of temporal machine learning models. Such models learn the aforementioned features themselves. We will use LSTM networks[48] and TCNs,[49] the latter being a specific variant of convolutional neural networks designed to handle time series.

On top, we will use the CKConv algorithm which has recently been developed in our consortium, which can cope with noisy data in a more robust way[50]. These approaches do not suffer from the disadvantage of the bias in feature design, however, do often require more data and usually lack insight. We will therefore combine these approaches with methods to gain insight into the concepts that have been learned, including LIME[51] and SHAP.[52] Our consortium has previous experience with both approaches in medical settings (see[34,35]).

Big (amount of) data

While the amount of data collected is enough to develop models based on logistic regression (as calculated before), more advanced machine learning models primarily thrive when data is abundant as applies to this study. While for low resource settings and our novel measurement device relatively limited data is available, there are rich and extensive datasets available from different (yet similar) settings that can act as a starting point for machine learning. These include the MIMIC dataset[53] and data collected in the Netherlands, Europe and three African datasets. We will start with the development of models based on these large datasets, and use it to: (1) identify the most important variables to incorporate in the models, also based on the constraints of the measurement device we will use; (2) identify the best features we can derive from these variables, and (3) act as a basic predictive model that we will later refine. To be able to reuse models derived from such datasets for our Malawian setting (for the selection of variables and engineering of features this is obvious) we will exploit the concept of transfer learning.[54] Hereby, we will take the pre-trained models and refine/improve them based on the data collected with our developed device.

Ultimately, we are interested in the generalisability of our models across the entire potential population of patients targeted with our approach. While a complete assessment is beyond the scope of this project, we will study generalisability in the following way: (1) we will develop models using data from one centre, and apply the found models to data from the second centre, and (2) we will study the generalisability in a setup where we do use patients from the same centre, but splitting the patients between a training and test portion, leaving the data of 30% of the patients out acting as an independent test set. Overall, we are confident that these approaches will deliver us a generalisable model. We will select the final model based on a combination of performance criteria as well as the level of insight that can be gained from the model.

Conventional Analysis

Although the primary aim is to develop a machine learning algorithm, additionally a conventional analysis will be performed and compared against the machine learning models.

A logistical regression model will be used to predict the onset of critical illness based on respiratory, circulatory, neurological, sepsis and admission related predictors. We will select variables in two different ways: expert opinion to select the most important 10 predictors based on literature or pathophysiological mechanisms, and backward elimination with the selection criterion of $p < 0.05$. Both approaches will be applied twice, once with only vital signs and once with vital signs and biomarkers.

The logistic regression models resulting from the two variable selection methods will be internally validated using 5-fold cross-validation. Performance metrics will be the area under the receiver-operating characteristic (AUROC), and calibration as assessed by calibration curve slope and intercept.

The performance of the conventional analysis will be compared to the machine learning approach by comparing the accuracy (sensitivity, specificity, positive and negative predictive value and AUC-ROC), c-statistics of the full model and additionally by decision curves and calibration plots.

The conventional and machine learning models will be validated by assessing their performance in the two study sites separately and by applying it on historical African datasets from the Gambia,[55] Kenya/Uganda[56] and Malawi.[40]

viii] Results Presentation

The results of the predictors and predictive models/algorithms will be expressed in tables (Odds ratios) and graphs (AUROC).

Performance metrics will be reported and display the area under the receiver-operating characteristic (AUROC), and calibration as assessed by calibration curve slope and intercept.

The performance of the conventional analysis will be compared to the machine learning approach by comparing the accuracy (sensitivity, specificity, positive and negative predictive value and AUROC), c-statistics of the full model and additionally by decision curves and calibration plots.

ix] Dissemination of the Results

Several strategies will be used to disseminate study results: at each stage of the data collection, dissemination meetings will be held with staff at Queen Elizabeth Central and Zomba Central; manuscripts will be prepared for submission to international peer-reviewed journals; the researchers will present findings at international conferences on (global) public health, implementation research, paediatric critical care and health economics; and the results will be compiled as part of the PhD theses.

Copies of all published articles, abstracts of conference presentations that result from the study will be submitted to the College of Medicine Research and Ethics Committee (KUHES REC); College of Medicine Library; The Health Sciences Research Committee (through the KUHES REC Secretariat); The University Research and Publication Committee (URPC) (through the KUHES REC Secretariat).

i] Ethical Considerations

Ethical approval

Full ethical clearance will be obtained from the College of Medicine Research and Ethics Committee (KUHES REC).

Informed authorities

Before data collection begins, relevant authorities will be informed about the exercise including the District Health Office (DHO), the hospital directors, the paediatric departments and the PMRA.

Informed Consent

All participants will undergo the written informed consent procedure, in which their parents or guardians will be required to provide a written consent, or thumbprint if illiterate, endorsing their voluntary participation. Each study participant will be given the option to take part or refuse. Those willing to participate will be informed about their right to withdraw at any point they feel they want to do so and informed that withdrawing from the study will have no bearing on access to health services. We will ask parents and/or children for permission at patient identification and before data collection. To allow for the obtaining consent we will not include children that need very urgent care such as resuscitation during admission/recruitment.

Payment for Participation

All data collection will be carried out during the hospitalisation. In return for their time and to support transport home after hospital discharge we will provide an equivalent of $5. No participants will be anticipated to return to hospital for research purposes exclusively, however if this would be the case an additional transport fee will be paid equivalent to $5. Patients recruited in the clinical pilot study may further benefit from both the close vital sign monitoring and the laboratory assays (blood culture, PCV and malaria slide results) which will be directly available to clinical staff.

Privacy and Confidentiality

The main ethical issues in this study relate to privacy and confidentiality. A detailed Data Management Plan will be available before the start of the research activities. The study team members will ensure that confidentiality is maintained. Care will be taken to ensure that the study data are stored in a secured (encrypted) storage environment to which only members of the study team have access. Access will be defined depending on the roles of the researchers. Respondents will be identified only by a participant ID number in transcripts. The study will comply with the General Data Protection Regulation (GDPR), which requires that personal data must not be kept as identifiable data for longer than necessary for the purposes concerned.

Risk Management and Safety

The observational study includes an e-CRF (annex 1b-d) completed by study nurses, a venous blood sample, a nasal swab and continuous monitoring. The sampling will potentially cause psychological distress to the children. We will try and minimise this by adequate training of study nurses prior to the study in these techniques and combine blood sampling with clinical sample taking if possible.

Vital signs monitoring is non-invasive, and this commonly applied technique in high income settings is generally well tolerated by (paediatric) patients. As we will make use of certified sensors there is no anticipated harm to the children. Potentially the alarms caused by the system may discomfort the guardians and child and may lead to earlier but also more interventions (e.g. start of oxygen, CPAP, nebulisation, antibiotics and blood culture, fluid bolus) which are meant to prevent critical illness, but in case of false positive alarms may unnecessarily discomfort the patients. For this reason the alarm limits are set at levels that will require

To reduce any potential impact on the delivery of critical care, all data collection will be conducted in coordination with hospital staff. In the case of guardians, the research team will pay special attention to the willingness of participants and will emphasise that participation in this study will not affect in any way the quality of care received.

Handling participant withdrawals

Participants will have the right to withdraw from the project at any time. If participants wish to withdraw from the project, they must contact the investigator, whose contact details are listed on the patient informed consent form of which they will receive a copy at enrolment. Upon this request, any primary data will be removed from the project.

j] Possible Constraints:

COVID-19 pandemic:

The health, safety and well-being of participants and researchers are paramount. The research team will adhere to the Malawian's public health guidelines, institutional policies and operate within guidelines endorsed by the Kamuzu University of Health Sciences ethics committee to assure safety and minimise risks to participants and researchers. A contingency plan to address the potential impacts of COVID-19 will be undertaken and reviewed as required. This will include an assessment of the possible data collection risks associated with COVID-19 transmission by the severity of harm (insignificant, minor, moderate, major and severe), and the likelihood of COVID-19 transmission (almost certain, likely, possible, unlikely and rare) across three key areas:

Priority

Assessment of the importance and risks of continuing the research as designed or with necessary modifications. Responses could include continuing the research in its present form, conducting the research in a modified form, suspending the research or closing the research.

Participation

Assessment of the ability of participants to participate in the research per protocol requirements and consideration of alternative models for participation that would not compromise the integrity of the study.

Capacity

Assessment of the resources available for continuing the research, including research staff, other support staff, space, equipment, supplies, etc.

k] Requirements:

Personnel

Each study site will have a team of five nurses to cover the unit 24/7. In addition a study assistant will support data collection, sample distribution and operation of the sites. A technician will ensure that all equipment is working properly, this work will be part of a MSc programme at MUBAS. The co-PI will oversee the performance of the teams. Two full time PhDs will perform the data and laboratory work during and after the project. The data PhD will also support the social science IMPALA study.

Data management

Large amounts of data will be stored and processed. Data will be entered on tablets and stored on a local server. The monitors and sensors will be facilitated by GOAL3. This equipment will remain in Malawi after the study for future use by the partners involved in this project.

Laboratory costs

Most laboratory work will be done in the laboratory of KUHES for which bench fees, freezer storage rental, consumables and specific analysis costs (PCR) have been allocated. For blood culture (and malaria testing), the routinely used facilities in ZCH and QECH will be used. This will allow the results to become available to the hospital clinicians and will benefit the patients. The budget allows us to pay for the extra costs this will cause.

Other costs

We will not ask patients to return to the hospital for this protocol, however we will reimburse guardians for their time. We aim to publish in open access journals and to disseminate the findings of our study and have budgeted for that. Lastly, we aim to train the study staff and hospital staff in the use of the monitor. The study staff will additionally get training in SOPs, GCP and critical care.

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4.1 SUBMISSION AND REVIEW OF THE PROPOSAL:

i] The Principal investigator shall prepare (4) copies of the proposal together with $100 processing fee or its equivalent.

ii] The copies shall reach the Secretary - KUHES REC 30 days before the date of the meeting.

iii] A letter from the respective head[s] of department(s) indicating that the research has the blessing of the department(s) shall be sent to the Secretariat together with the proposal. Research affiliations like Wellcome Trust, John Hopkins Project etc need a supporting letter from Head of Department.

iv] Everything should go through the head of department including resubmissions.

v] A copy of a brief CV of each of the investigators shall be sent to the Secretariat [1 copy of each]. (Except those which have been submitted within the same academic year)

vi] Within two weeks receipt of the proposal will be acknowledged in writing.

vii] Following the review, the results together with comments from the Research Committee will be sent to the Principal investigator within two week. This response will include - how to proceed e.g. resubmission or response for specific issues.

viii] Resubmission shall also be at least two weeks before the following meeting.

ix] Research affiliations need a supporting letter from the head of department.

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Annexes

1. E-CRFs
    a. Patient identification forms (Paper)
    b. Recruitment Form (e-CRF)
    c. Daily Sheets (e-CRF)
    d. Outcome Form (e-CRF)
2. Informed consent forms
    a. English
    b. Chichewa
3. MTA
4. CV´s investigators
5. Medical registration investigators
6. Support letters departments-hospitals
    a. Dep op paediatrics and child health-Blantyre
    b. Hospital research committee Blantyre
    c. Zomba Central Hospital