I. Study Title

Pilot clinical assessment of low-cost infant incubator in monitoring temperature and treating hypothermia in infants.

Investigators

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Institutions under whose umbrella the research project will be conducted

College of Medicine, Blantyre, Malawi

Rice University, Houston, TX, USA

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II. Abstract

Hypothermia is recognized as one of the leading causes of neonatal mortality in low resource settings [1] and is especially common among premature babies [2]. In high-resource settings, the standard treatment for hypothermia is the use of an infant incubator or radiant warmer which can provide closely regulated warmth to a single infant. However, these devices are expensive, sensitive to fluctuations in electrical power, and can require disposible or fragile components. Because of this, in low resource settings, there is limited equipment available for the warming of hypothermic infants. This is compounded by the fact that there are also limited tools for monitoring infants' temperatures, making it difficult to identify which infants are in need of thermal care and provide them with individualized treatment. When skin to skin contact, or Kangaroo Mother Care, is not feasible, the treatment available at Queen Elizabeth Central Hospital (QECH) is the Hot Cot, a low cost device that provides individualized heat but requires constant monitoring from the clinician to prevent overheating.

A team of researchers at Rice University and QECH are working to develop a low-cost infant incubator called "IncuBaby" that consists of two components: a temperature sensor that can continuously monitor an infant's temperature, and a heated, enclosed area that can adjust internal temperature based on the feedback from the temperature sensor. This robust, low-cost device will allow for the individualized treatment of hypothermia with minimal intervention from the clinical staff. A reusable band to hold the temperature sensor will eliminate disposable components.

In this study, we intend to evaluate the efficacy of this incubator at QECH by comparing infants' temperatures before and after treatment, and calculating the proportion of time that the infants remain in a normothermic range after rewarming. This is a pilot prospective study taking place in the neonatal ward (Chatinkha) at Queen Elizabeth Central Hospital . Up to 60 infants in need of temperature monitoring or thermal care will be enrolled in the study. During phase I of this study, the infants will be continuously monitored using the IncuBaby temperature sensor and a gold standard temperature monitor for up to 3 days. The accuracy of the IncuBaby temperature sensor will be determined by calculating the difference between the temperatures recorded by the temperature sensor and the commercial patient monitor at each point in time. Our target error is less than +/- 0.5 C.

During phase II of the study, infants in need of thermal care with an incubator will be treated with an IncuBaby device and their temperatures will be continuously monitored by both the temperature sensor of the IncuBaby device and a commercially available patient monitor. Care will continue at the clinician's discretion until the infant can be weaned from the incubator or until patients are withdrawn from the study and placed on the standard of care. To determine the effectiveness of the IncuBaby device at warming infants, the temperatures of the infants will be compared before and after treatment for each subject. The proportion of time the device maintains the subject's temperature in a normal range will also be calculated.

The data collected here will be used to evaluate the use of the IncuBaby device as a treatment for neonatal hypothermia. The results of this study will be made available to the Ministry of Health, NHSRC, COMREC, the College of Medicine Library, the Department of Paediatrics, and other partners working in neonatal and child health. Findings will be published in academic journals and conference proceedings in an effort to disseminate results to potential end-users.

III. Background and Justification

Neonatal hypothermia is a ***pervasive global challenge***; as many as 85% of infants born in hospitals in low-resource settings are too cold (defined as a temperature <36.5C) [3]. A recent study of 23,240 newborns in Nepal showed that babies with moderate hypothermia are nearly five times more likely to die than normothermic infants; the risk of death is more than 23 times higher for babies with severe hypothermia [4]. Kangaroo Mother Care, while effective, is not always a feasible method of thermal care due to outstanding medical conditions in the infant or mother.

Robust and low-cost technologies that aid in the safe treatment of hypothermia are essential devices that will equip clinicians for complete thermal care of infants and lower the mortality rate from this condition. Rice is collaborating with Malawian clinicians to design IncuBaby - a low-cost infant incubator that can adjust the temperature inside the incubator based on the infant's temperature. This device is different from traditional incubators in that it is low-cost, resistant to electrical surges, very simple to use, and does not require any disposable parts. It is different from existing low-cost devices in Malawi in its ability to automatically regulate the temperature of the baby, preventing both hypothermia and overheating. This pilot study is designed to test the efficacy of the IncuBaby device by measuring its ability to both warm infants and maintain their temperatures in a normothermic range.

IV. Literature Review

Hypothermia is one of the leading causes of neonatal mortality in low resource settings [1]. It is especially common in premature infants who have increased difficulty maintaining their core body temperatures in the small optimal range [1, 4]. In many resource-limited settings, the prevalence is high but poorly documented, with reported cases occurring in 32 to 85% of infants born in hospitals [6]. In 2013, more than 2.7 million child deaths occurred in the neonatal period [7]. Many of the most common causes of death are associated with hypothermia, which is often listed as a comorbid condition [6]. Thermal care is therefore an important component of mitigating the effects of neonatal illnesses and complications [6].

Malawi has the highest rate of premature births in the world (18.1 per 100 live births), but limited equipment for thermal care [2]. Incubators and patient monitors can provide precise thermal treatment and close monitoring that allows for the prevention and treatment of hypothermia [5]. However, due to shortages of equipment and high patient to staff ratios, infants in Malawi have their temperature taken only once or twice a day. Because of this, hypothermia can often go undetected and progress rapidly before treatment starts. Once detected, there are limited treatment options for hypothermia [7]. Kangaroo Mother Care (KMC), or skin to skin contact, is the recommended method of thermal care for mild hypothermia [7]. KMC is effective for warming but is not always feasible due to medical complications in the mother or infant, the mother's additional responsibilities, or limited facility space and support [8, 9, 10]. Incubators or radiant warmers are used for treating moderate and severe hypothermia but are often not available as they are very expensive [7]. Those that are available often break and are difficult to fix. Temperature monitoring for these devices often require delicate probes and disposable stickers, which are difficult to acquire and maintain. Queen Elizabeth Central Hospital NICU has several "Hot Cots" available. The Hot Cot is locally manufactured and consists of a wooden crib with four lightbulbs that can be turned on and off manually to provide warmth to the infant [7]. However, a

manual method of heating is difficult to regulate with already overburdened staff, and several instances of overheating have occurred.

With feedback from Malawian clinicians, Rice engineers have designed IncuBaby - a low-cost infant incubator with automatic temperature regulation. It is low-cost and robust like the Hot Cot, but requires less active monitoring by the user because it incorporates continuous temperature monitoring to ensure the temperature of the incubator is appropriate. It utilizes the Rice-designed neonatal temperature monitor to take the infant's temperature, and uses that information to adjust the heat in the incubator accordingly.

Previous Clinical Trials

The temperature sensor consists of a stretchy "belt" that wraps around the abdomen of the infant and senses temperature through a small stainless steel sensor. The belt and sensor can be easily cleaned between uses using a bleach solution. As even mild hypothermia (temperature of 36-36.5 ° C) is associated with a 1.8 fold increase in risk of mortality [4], our target accuracy for temperature monitoring is ± 0.5ºC. We have shown that NTM meets this standard in two settings through two clinical trials conducted in Houston, TX. First, we evaluated NTM's accuracy compared to a Phillips Intellivue patient monitor temperature probe in healthy adults; results show temperatures measured with NTM are within ±0.3ºC compared to the commercial monitor. A similar evaluation of NTM monitoring infants in a daycare showed that results within ±0.5 ºC of the commercial monitor. These studies showed promising accuracy results, and improvements have been made to the sensor to ensure reliable temperature readings in infants.

Benchtop Testing

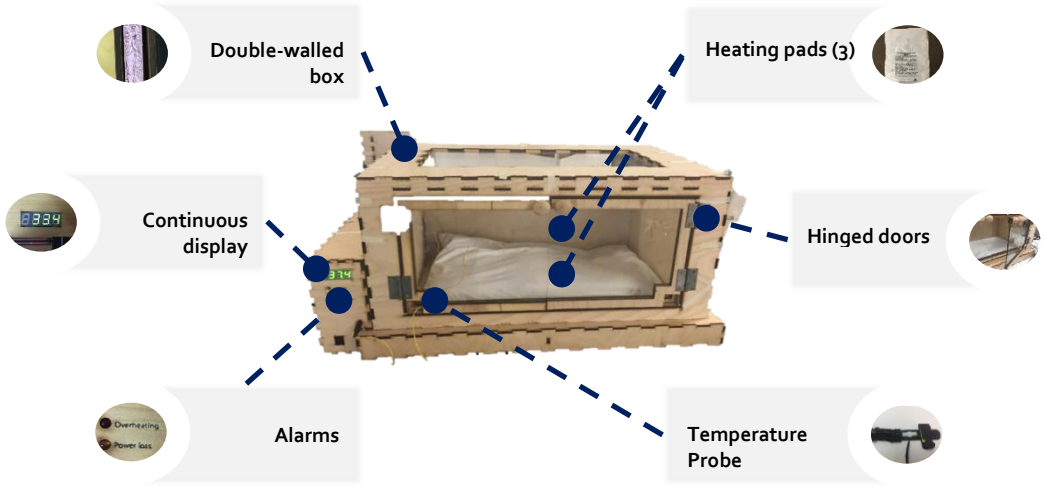
The incubator has undergone extensive benchtop testing at Rice University. The International Electrotechnical Commission (IEC) Standards for incubators (IEC 60601-2-19) were used to define the testing protocols and pass criteria. The standards for warming mattresses (IEC 80601-2-35) were also considered as the incubator provides heat to the infant through a combined mechanism of warming the mattress and warming the air. The results of the tests are summarized in the table below.

Specification	Current Performance	IEC Criteria	IEC Reference
Overshoot	<0.3ºC	<2ºC	201.12.1.108
Control Accuracy	+/- 0.35ºC	+/- 0.7ºC	201.12.1.104
Probe Accuracy	+/- 0.1ºC	+/- 0.3 C	201.12.1.103
Temperature Stability	+/- 0.35ºC	+/- 0.5ºC	201.12.1.101
Temperature Uniformity	+/- 0.8ºC	+/- 0.8ºC	201.12.1.102
CO2 %	<0.2%	<0.5%	201.12.4.2.101

In addition to conducting these tests according to the IEC protocols, additional efforts were made to simulate the warming of an infant in the IncuBaby device. A thermal model of an infant was

created using a 1.5 L water bottle and small aquarium heater and pump. This model, called SimuBaby, could be set to different temperatures to simulate varying degrees of hypothermia. Tests with SimuBaby confirmed that the IncuBaby device could slowly rewarm an infant at a controlled rate of 0.5 C/hr.

The IncuBaby device is constructed from plywood sealed with a non-toxic VOC-free waterproof sealant. The plywood forms a double walled wooden box. Heat is provided via unmodified, commercially available electric heating pads located inside the walls. All heating elements are shielded from patients. Foam insulation and a reflective radiant barrier are also included inside the walls to improve heat retention in the event of a power loss. The incubator is equipped with three temperature sensors in addition to the sensor connected to the baby. The baby sensor provides the primary method of temperature regulation. The incubator limits the change in the infant's body temperature to 0.5C/hour. Faster changes in temperature have been demonstrated to be clinically unsafe for thermally unstable infants [I will find a source for this].Additional sensors monitor the temperature at various points in the incubator to ensure a safe environment at all times. One of these sensors monitors the surface temperature of the incubator, limiting it to 41 C, which is below the IEC maximum surface temperature of 43 C. This results in a maximum air temperature of 36 C.



A third party electrical safety check will be performed by biomedical technicians at Texas Children's Hospital in Houston, TX before the devices are transported to Malawi. Upon arrival, we will request that Physical Assets Management (PAM) perform brief testing on the devices using their checklist for infant warming devices.

V. Hypotheses

The purpose of this study is to determine if the IncuBaby device can reduce instances of hypothermia in neonates at risk of hypothermia in low-resource settings by evaluating its ability to warm an infant and regulate its temperature within a normothermic range. Specifically, we will test whether the IncuBaby device can warm a hypothermic infant to a normothermic temperature by comparing their temperature before and after treatment. Further, we will test whether the IncuBaby device can be used to regulate the temperature of an infant at risk for hypothermia within a normothermic range by calculating the proportion of time that each subject remains in the

normothermic range (e.g. not hypo-/hyper-thermic). We expect that infants treated with the IncuBaby device will be warmed to a normothermic range without risk of hyperthermia.

VI. Objectives

The goal of this work is to reduce instances of hypothermia in at-risk infants in the neonatal ward at QECH. To this end, we will examine both the accuracy and the safety of the IncuBaby device.

1. Primary Efficacy Objectives:
    a. To compare the accuracy of the IncuBaby temperature monitor to a commercial vital signs monitor, the gold standard for continuous monitoring.
    b. To evaluate the ability of IncuBaby to warm a hypothermic infant and maintain an infant's temperature within the normothermic range

2. Primary Safety Objective:
    a. To determine the ability of the temperature monitor to alert clinicians to the presence of hypo-/hyperthermia
    b. To ensure that IncuBaby is easy to understand and use

VII. Methodology

A. Study Type

This is a two-phase, **pilot prospective study** to determine the effectiveness of a low-cost incubator in warming infants and regulating their temperatures. The temperature sensor that controls the heat of the incubator based on the infant's temperature has been previously evaluated in Rice IRB approved studies in Houston, TX. The first phase will validate the use of the temperature sensor in infants by comparing it to a commercial temperature monitor. The second phase will test the effectiveness of the IncuBaby device using that temperature sensor to regulate the heat provided by the incubator.

B. Place of Study

This clinical study will take place at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. Patients will be recruited as they are identified as being in need of thermal care that cannot be provided by KMC.

C. Study Period

Data collection will begin at QECH following study approval by the NHSRC. In total, we anticipate data collection for this study will take approximately 3-6 months.

D. Sample Size and Inclusion Criteria

This study will enroll up to 60 infants at Queen Elizabeth Central Hospital in two phases. Up to 30 subjects will be collected for phase I and 30 subjects for phase II. All subjects in both phases will be monitored with a gold standard commercial monitor in addition to the treatments described below.

The estimate for Phase I was based on the IEC standard for temperature monitors, which requests at least 15 subjects that are between 0 and 3 months of age. Additional subjects are requested here to account a range of weights (preterm, full-term), temperatures (hypo-, normo-, hyperthermic), and treatment locations (open cot, radiant warmer), as well as any missing records. Infants enrolled in this phase of the study will be treated according to the standard of care at QECH.

The estimate for phase II was based on temperature data collected from infants at QECH during a pilot study of the Pumani CPAP device, which shows that infants receiving CPAP at QECH had an average temperature of 36.1 C, which is outside the normothermic range. A power analysis of a comparison of means was performed using the CPAP data as a control group. It showed that at least 14 IncuBaby subjects are needed to demonstrate that the IncuBaby treatment results in an average temperature of 36.5 C (normothermic) with a p value of 0.05. 30 subjects are requested to account for the difference in patient populations (preterm, full-term, RDS) as well as any lost or missing records. All babies who are eligible for and enrolled in this phase of the study will be treated using the IncuBaby device. Previously-collected temperature data and Phase I data will be treated as control data for the purpose of analysis.

Inclusion criteria:

1. The subject is currently being treated at QECH in the neonatal ward.

2. An IncuBaby device and study monitor are available for use.

3. The subject's caregiver has provided informed consent for their child to participate (consent form attached to this proposal).

4. Phase II only: the subject is eligible for thermal care in an incubator. If the subject is recommended for KMC, they will not be eligible for participation in this study. To be considered for care with the IncuBaby, infants should be:
    - Less than 1000 g
    - Or > 1000 g but
        - Receiving medical interventions such as CPAP, oxygen, phototherapy, or IV
        - Unstable, critically ill or surgical conditions
        - No mother or caregiver available for KMC
        - Mother too sick to provide KMC
        - Clinician in charge has decided against KMC as requires closer supervision by nursing staff
        - No space in KMC

The subject may be excluded from the study at the clinician's discretion for any reason including potential for skin irritation, cough or other condition that may preclude use of the temperature belt, or concurrent treatments that may require increased patient care. Only subjects eligible for care in an incubator will be enrolled in phase II.

If a patient is not enrolled in the study, the patient will receive the standard of care.

Informed Consent (consent form attached to this proposal in both English and Chichewa):

The investigator will provide details of the study to all eligible subjects' guardian and answer all questions. Fully informed and signed consents will be obtained from the subject's guardian prior to the start of any study procedures.

Documentation of the consent process will include the following elements:

• Date and time of consent;

• Topics discussed with the subject's guardian (e.g. risk, benefits, etc.); and

• Confirmation that the consent was reviewed, that the guardian's questions were answered, and that a signed copy of the consent was provided to the subject's guardian.

Potential Benefits and Compensation of the Proposed Research to Human Subjects and Others: Neonates and infants at risk for hypothermia may benefit from participating in this study as alternative forms of accurate monitoring and treatment may not be readily available. This study may benefit infants in the future as the IncuBaby device may enable cost-effective, accurate detection and treatment of hypothermia.

E. Data Collection and Analysis

Training:

1. Prior to the start of the study, all study nurses/clinicians will receive training on how to use the temperature probe, IncuBaby device, and commercial study monitors. The study nurse/clinician will apply the temperature sensors to the infant.
2. A Rice researcher will be available for the duration of the study to record the data from the monitors.

Enrollment :

Enrollment will take place after fully informed and written consent from the parent or guardian. Enrollment in Phase II of the study will only begin after Phase I is complete. A parent will be free to withdraw their child from participating at any time, without explanation and without detriment to ongoing care. There will be no financial benefit to participants though the infants will benefit from close monitoring. A participant identification number will be assigned. This number will be used for identification purposes throughout the study.

Treatment and Monitoring of Neonates:

During **Phase I**, the following steps will be taken:

A trained study nurse will assess the subject for clinical complications before attaching the temperature monitoring device.

1) A trained study nurse or clinician will attach the temperature monitoring device to the infant. A trained research assistant from Rice University or from the Biomedical Engineering Department at Malawi Polytechnic will observe all procedures and will notify the nurse of any observed errors so they may be corrected. They will also be able to answer any technical questions from the nurse.
2) The trained study nurse will attach the temperature probe from the commercial patient monitor as well as provide any other care needed.
3) A research assistant will use a laptop to collect the electrical signals from both temperature monitors.
4) Temperature monitoring will continue for up to 3 days. The research assistant may ask the nurse to remove and reapply the temperature monitor during this period.

Once Phase I is complete, Phase II will begin. During Phase II, the following steps will be taken:

A trained study nurse will assess the subject for clinical complications before beginning treatment.

1) A trained study nurse or research technician will turn the incubator on to begin pre-warming.
2) A trained study nurse or clinician will attach the temperature probe from the IncuBaby device to the infant and then place the infant in the incubator. A trained research assistant from Rice University or from the Biomedical Engineering Department at Malawi Polytechnic will observe all procedures and will notify the nurse of any observed errors so they may be corrected. They will also be able to answer any technical questions from the nurse.
3) The trained study nurse will attach the temperature probe from the commercial patient monitor as well as provide any other care needed.
4) A research assistant will use a laptop to collect the data from both devices.
5) Care will be continued at the discretion of the clinician until the infant can be weaned from the IncuBaby device. The infant may be weaned to the standard of care or end thermal treatment. The infant will be transitioned to KMC as soon as possible after these eligibility criteria are fulfilled:
    - Completed other treatment (CPAP, phototherapy, IV)
    - Mom/caregiver becomes available
    - Weight increases > 1000g
    - Become clinically stable
    - Body temperature is stable and not dipping below normal despite thermal support

Based on the discretion of the clinician, the subject may be weaned to KMC or an open cot. The IncuBaby device has a “weaning” setting that turns off the heaters in the incubator but continues to monitor the infant’s temperature. If the infant is found to be hypothermic after ending treatment and the clinician recommends continued incubator care, the subject may recommence use of the IncuBaby for treatment.

The commercial patient monitor will alert nursing staff if the baby’s temperature becomes too high or too low. Temperature settings for alarms will be set by a clinician so that the high temperature

alarm is > 37.5 C, and the low temperature alarm is < 36.5 C. During Phase II, the following steps will be recommended if the commercial patient monitor sounds a high or low temperature alarm. These guidelines were written in accordance with current clinical practice at QECH. The study nurse can also choose to discontinue the use of the IncuBaby device at any time.

High temperature alarm – indicates possible hyperthermia

- Check that the incubator temperature is at 36C or less.
- Open the incubator and recheck the baby's temperature
- If baby's temperature is still above normal remove blankets/clothing
- If baby is febrile despite these measures look for a clinical reason for the temperature
- Remove the infant from the IncuBaby device

Low temperature alarm – indicates possible hypothermia

- Check that the incubator is in on and functioning
- Check that the temperature probe has not fallen off.
- Recheck the baby's temperature
- If temperature still low add blankets/clothing and hat
- If the temperature is still low look for a clinical reason for the hypothermia

During both phases, a research assistant will be available during the trial to mitigate any complications with the device. A nurse will be available to respond to alarms from the continuous patient monitor. If the subject's guardian, the nurse, or the research assistant indicates concern during the tests, the study treatment can be discontinued and the subject will return to the standard of care.

Intended Data Collection:

Clinical data will be collected on paper forms as is consistent with current clinical practice. Data will be saved on a secure study server for analysis. Clinical and/or research personnel will record information, excluding personal identifiers, on a standardized patient monitoring form. After the subject's participation is complete, a research assistant will collect and scan the form. We will collect the following information:

1. Baseline demographic and relevant medical information
    a. Recorded once at enrollment
        i. Date of Study
        ii. Date of Birth
        iii. Sex
        iv. Birth Weight
        v. Type of delivery
        vi. Gestational age at birth
        vii. Corrected gestational age
        viii. Abdominal circumference
        ix. Admission Temperature
    b. Recorded throughout study as clinically collected
        i. Other comorbidities
        ii. Medications/treatments given
        iii. Current weight
        iv. Temperature measurements taken as standard of care

2. Accuracy
    a. Recorded automatically by study equipment
        i. Abdominal temperature from IncuBaby temperature probe and gold standard device
        ii. Alarms
        iii. Temperature in incubator*
        iv. CO2 levels in incubator*
        v. Humidity levels in incubator*
    b. Movement/other caregiving
    c. Fit/tightness of the strap
    d. Ambient temperature

**Phase II only*

A log of an observed user error or comments about the device will be used to improve future iterations of the device. The nurse and technician monitoring forms that will be used to record the above variables are attached to this proposal.

Data Management and Analysis:

Personal identifiers will be removed from the data which will be kept on a secure server accessible only to study personnel.

The accuracy of the IncuBaby temperature sensor will be determined by calculating the difference between the temperatures recorded by the temperature sensor and the commercial patient monitor at each point in time. The average error between the temperature sensor and the gold standard will be calculated for each subject and compiled in a Bland-Altman plot. The 95% limits of agreement will be calculated. Our target error is less than +/- 0.5 C.

As a secondary analysis, the errors will be plotted against strap tightness and ambient temperature to determine their confounding effects on accuracy. An ANOVA will be used to determine statistical significance.

To determine the effectiveness of the IncuBaby device at warming infants, the temperatures of the infants will be compared before and after treatment for each subject. These values may also be compared to infants not treated with IncuBaby as a control group. A comparison of the means will be used to show statistical significance between the two groups.

To determine the ability of the IncuBaby device to regulate the infants' temperatures, the proportion of time that each subject remained in a normothermic range will be calculated. This proportion will be compared to literature values for incubators and radiant warmers as well as infants not treated with IncuBaby. A similar comparison of the means will be used to show statistical significance. This analysis will show how effective IncuBaby is at warming patients, and how well it is at regulating their temperatures.

The research team from Rice University and QECH will be responsible for all data analysis. We plan to analyze data using Excel, MATLAB, and associated statistics packages.

VIII. Dissemination of results

The ability of IncuBaby to warm infants and regulate their temperatures will be shown through tables and graphs using the methods described above. Tables will be used to display the clinical outcomes and functionality of the alarm systems. Tables and graphs may also be used to show any additional correlations, explain outliers, or demonstrate confounding effects.

The results of this study will be made available to the Ministry of Health, COMREC, the College of Medicine Library, the Department of Paediatrics, and other partners working in neonatal and child health. A copy of the final report and any published papers or abstracts will be submitted to The Health Sciences Research Committee and the University Research and Publication Committee (URPC) through the COMREC Secretariat. Findings will be published in academic journals and conference proceedings in an effort to disseminate results to potential end-users. The research findings of this study will be critical in the evaluation of future interventions.

IX. Ethical considerations

A. Protection of Human Subjects

All studies involving human subjects will be conducted in a manner that will minimize the risk to the individual, utilize all patient materials for scientifically meaningful purposes, and protect individual rights to confidentiality. The associated clinical protocols will be approved by the Malawi NHSRC, Lilongwe, Malawi and by the Institutional Review Board of Rice University, Houston, TX. All researchers will conform to the standards set forth by the National Institutes of Health regarding experiments involving human subjects.

B. Potential Benefits of the Proposed Research to Human Subjects and Others

Infants experiencing hypothermia may benefit from participating in this study since the IncuBaby device allows for slow rewarming of the infant using continuous feedback from the temperature sensor. Subjects will also benefit from extra monitoring from the gold standard temperature probe which includes alarms for hypo- and hypothermia, and care from dedicated study nurses. Others may benefit from this study in the future as IncuBaby is a new low cost and robust incubator that can be used to treat hypothermia.

C. Protection Against Risk

To protect against the risks of hypo- and hyperthermia, the temperature of the subject will be monitored continuously by a commercial patient monitoring device and the subject will be removed if the temperature varies from expected conditions. The commercially available device uses a temperature probe accurate to +/- 0.1 C and includes alarms for both hypo- and hyperthermia. The specific level of these alarms can be set by the clinician according to the specific needs of the subject depending on their age and weight. The incubator temperature will be continuously monitored by separate temperature probes included with the device. The CO2

levels in the incubator will also be monitored using a commercially available CO2 monitor. Axillary temperature measurements given as the standard of care will continue to further monitor the infant during treatment. At any point during the treatment, the nurse may remove the patient from the study device and continue treatment with the hospital's standard of care. For infection control, after each subject, the IncuBaby device will be cleaned thoroughly with a bleach solution.

The subject may be removed from the study at any time at the request of the parents or clinicians.

There is the potential risk of the loss of confidentiality associated with participation in this study. No patient identifiers will be collected by the study. All patient data will be assigned a number to ensure subject confidentiality. All efforts will be made to maintain strict patient confidentiality.
All studies involving human subjects will be conducted in a manner that will minimize the risk to the individual, utilize all patient materials for scientifically meaningful purposes, and protect individual rights to confidentiality. The associated clinical protocols will be approved by COMREC in Malawi and by the Institutional Review Board of Rice University, Houston, TX. All researchers will conform to the standards set forth by the National Institutes of Health regarding experiments involving human subjects.

The co-investigators will take the following steps to protect the participant's identities during this study: (1) Each participant will be assigned a number; (2) The co-investigators will record any data collected during the study with this number and not by name; (3) Any original data files, as well as the informed consent forms, will be stored in a locked cabinet in the PI's office space. All data will be recorded in a password-protected database. Only the investigators listed in this study will have access to the data, and if the data is published at any time in the future, it will be reported collectively with no reference to the subjects' identities.

X. Personnel and Institution

A. Investigators

Principal Investigators: Dr. Queen Dube, Department of Paediatrics, QECH, Blantyre, Malawi

Co-Investigators: Rebecca Richards-Kortum, PhD, Dept of Bioengineering, Rice University, Houston, TX USA

Maria Oden, PhD, Dept. of Bioengineering, Rice University, Houston, TX, USA

Megan Heenan, PhD, Rice 360: Institute for Global Health, Houston TX, USA

Mary Kate Hardy, Rice 360: Institute for Global Health, Houston TX, USA

Rebecca Selle, Rice 360: Institute for Global Health, Houston TX, USA

Prince Mtenthaonga, Rice 360: Institute for Global Health

As head of Paediatrics at Queen Elizabeth Central Hospital in Malawi, Dr. Queen Dube worked with Rice University to help develop IncuBaby to treat infants at risk for hypothermia. Dr. Dube will oversee all aspects of this project, including clinical aspects, development and implementation of training materials, outreach to hospitals, and the development of the training video for maternity wards across Malawi.

Drs. Oden and Richards-Kortum have more than 20 years of experience in medical device design, and focus on developing and implementing appropriate health technologies for low-resource settings. They have led the development of IncuBaby, including incorporating design refinements, working with the team from Queen Elizabeth Central Hospital to design training programs, and developing testing requirements and protocols.

Prince Mtenthaonga will act as the primary study nurse. In addition to providing clinical support during the study, he will coordinate nurse schedules as necessary for extended period of monitoring during clinical testing. He has assisted in two clinical trials involving Rice360 devices at QECH and received his Bachelor of Science in Nursing and Midwifery from the University of Malawi-Kamuzu.

B. Institutions under whose umbrella the research project will be conducted

College of Medicine, Blantyre, Malawi and Rice University, Houston, TX, USA

XI. Work plan

Work performed at QECH will be directed by Dr. Queen Dube. She will oversee all aspects of this project, including clinical aspects and testing.

Dr. Rebecca Richards-Kortum and Dr. Maria Oden at Rice University will be responsible for overseeing data analysis and monitor data collection.

The local researchers will be available by phone, email, and site visits to respond to any questions and/or concerns. The US based researchers will be in frequent contact with the local team.

<table>
<tr><th colspan="3">Pilot IncuBaby Trial: Timeline</th></tr>
<tr><th></th><th>Phase I: temperature monitoring</th><th>Phase II: hypothermia treatment</th></tr>
<tr><td rowspan="4">Month 1</td><td>Setup in neonatal ward</td><td rowspan="5"></td></tr>
<tr><td>Test initial subjects</td></tr>
<tr><td>Nurse/technician training</td></tr>
<tr><td rowspan="2">Testing - monitor temperatures in a range of infants</td></tr>
<tr><td rowspan="2">Month 2</td></tr>
<tr><td>Evaluate sensor accuracy</td></tr>
<tr><td rowspan="2">Month 3</td><td rowspan="3"></td><td>Incubator training and setup</td></tr>
<tr><td rowspan="2">Testing - monitor temperatures and use incubaby device as warming tool</td></tr>
<tr><td>Month 4</td></tr>
<tr><td>Month 5</td><td colspan="2">Data Analysis (at Rice University)</td></tr>
</table>

XII. Budget

Salary Description	Cost
Queen Dube Honorarium	$9,090
Direct Costs Total	$9,090
10% F&A Costs	$909
Total	$10,000

XIII. Budget Justification

Temperature monitors, IncuBaby devices and paper forms (consents and monitoring forms) will be provided by Rice University. We have received funding from private sources to support this study which provides both the honorarium to Dr. Dube and the 10% F&A costs. All other work will be completed at Rice University.

XIV. Bibliography

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