A. Title

Assessment of low-cost temperature monitoring tools for neonates.

B. Investigators

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Investigators' CVs: Please see Appendix 1

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

[i] College of Medicine, Blantyre, Malawi
[ii] Rice University, Houston, TX, USA

D. Executive summary

Problem statement: 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) [1]. 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 [2]. While the risks of being too cold are well recognized, hypothermia remains a largely invisible problem in overcrowded newborn units in low-resource settings. Electronic temperature monitors used in high resource settings are not available in low-resource settings because they are too costly or require a constant supply of consumable thermistors. Simple digital or analog thermometers are often unavailable; when they are available, wards are often too short-staffed to permit routine monitoring at regular intervals.

Aim of Study: A team of researchers at Rice University and QECH are working to develop a low-cost temperature sensor that can continuously monitor an infant's temperature (NTM). This robust, low-cost device will allow for the individualized monitoring of each infant with alerts for hypo and hyperthermia. A reusable band to

hold the temperature sensor will eliminate disposable components. This study will assess the accuracy of this novel device against a gold standard along with existing low cost temperature monitors, ThermoSpot and Bempu, to determine which tool is most accurate and effective for neonatal wards.

Specific objectives: In this study, we intend to evaluate the accuracy of these devices at Queen Elizabeth Central Hospital (QECH) by comparing the temperature readings to a commercially available gold standard device. We also want to ensure the devices are easy to understand and use and could be implemented in the wards.

The specific objectives are:

1. To determine the accuracy of the NTM, Bempu, and ThermoSpot devices when used by nurses in the neonatal ward by comparing
    a. Continuous temperature measurements
    b. Periodic temperature measurements
    c. Temperature during alarm events
2. To ensure the NTM is easy to understand and use in the
    a. Nursery with open cots, hot cots, and radiant warmers
    b. KMC ward

Methodology: This is a method comparison study taking place in the neonatal ward (Chatinkha) and KMC ward at Queen Elizabeth Central Hospital (QECH). Up to 60 infants in need of temperature monitoring or thermal care will be enrolled in the study. The infants will be continuously monitored using the NTM, Bempu, ThermoSpot, and a gold standard temperature monitor for up to 3 days. The accuracy of the devices will be determined by calculating the difference between the temperatures recorded by the test devices and the commercial patient monitor at each point in time. Our target error is less than +/- 0.5 C.

Implications of the study and dissemination plans: The data collected here will be used to evaluate the use of the temperature monitoring devices as tools for monitoring and diagnosing hypothermia. The results of this study will be made available to our partners working in neontal and child health. Findings will be published in academic journals and conference proceedings in an effort to disseminate results to potential end-users.

E. Background Information and Introduction

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) [1]. 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 [2].

While the risks of being too cold are well recognized, hypothermia remains a largely invisible problem in overcrowded newborn units in low-resource settings. Data show that

babies who suffer from even mild hypothermia are at increased risk of jaundice, sepsis, hypoglycemia [3], and death [2]; unfortunately, there are no visible signs of mild hypothermia and risks become significant long before a baby begins to feel cold to the touch. Hyperthermia is equally devastating- and sometimes can be caused by attempts to warm a baby without monitoring her temperature carefully. Additionally, large swings in temperature–known as thermal shock–can lead to negative outcomes, including death. Constant maintenance of infant temperature within a very tight range is therefore imperative [4]. Electronic temperature monitors used in high resource settings are not available in low-resource settings because they are too costly or require a constant supply of consumable thermistors. Simple digital or analog thermometers are often unavailable; when they are available, wards are often too short-staffed to permit routine monitoring at regular intervals.

Although temperature monitoring is both a critical component of neonatal care and also a well-documented challenge, there is no broad consensus on the best method to monitor temperature in low-resource settings. **We have developed a new device called NTM: a simple, affordable ($10), and rugged tool to continuously monitor and display neonatal temperature, providing a rapid way to alert clinical staff and mothers to periods of hypo- or hyperthermia.** As shown in **Table 1**, NTM is a reusable temperature sensor attached to an infant's abdomen to detect core body temperature. It 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.

Even mild hypothermia (temperature of 36-36.5 ^{o} C) is associated with a 1.8 fold increase in risk of mortality [2], thus our target accuracy for temperature monitoring is ± 0.5^{o}C. We have shown that NTM meets this standard in two settings through two IRB-approved studies 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 0.3^{o}C compared to the gold standard. A similar evaluation of NTM monitoring infants in a daycare (subjects <18 months) showed that results within 0.5 ^{o}C of the gold standard.

The user interface of the device was designed with feedback from Malawian doctors and nurses. The baby's temperature is displayed continuously on the battery powered control box; if the infant's temperature drops below 36.5 ^{o}C, a blue light atop the box flashes to signal that intervention is necessary. Similarly, if the infant's temperature exceeds 37.5 ^{o}C, a red light flashes signaling for intervention. The light flashes speed up with degree of hypo- or hyperthermia.

NTM has important advantages compared to two other approaches which have been developed to address this need (Table 1). Unlike Bempu, a wrist-worn monitor that provides an audible alarm, NTM is placed over the liver to measure core temperatue and it displays temperature continuously. Neonatal nurses on our development team identified

Table 1: Options for low cost neonatal temperature monitoring			
	NTM	**Bempu**	**ThermoSpot**
			
Benefits	Easy to understand continuous visual cues and digital temperature display, no disposables	Audiovisual alarm, intuitive, also suitable for in home use	Visual cue for different levels of hypothermia, low cost, no power required
Cost	$10	$30 (2000 Rs) Bempu.com	$0.50 Maternova.net

continuous display of temperature as one of the most highly desired features of NTM because it would help improve the care they can provide while reducing their workload. Thermospot, a temperature sensitive sticker, is another alternative to monitor neonatal temperature. While Thermospot changes color to indicate temperature (green at temperatures above 36.5^{o}C, brown between 35.5 and 36.4^{o}C, and black below 35.5^{o}C) it is not reusable and the color change can go unnoticed without scheduled monitoring.

In this study we plan to evaluate the ability of NTM, Bempu, and ThermoSpot to detect hypo- and hyperthermia in neonates by comparing to a gold standard electronic temperature monitor used in high-resource settings.

F. Rationale/Justification for the research project

Together, prematurity and infection account for more than 50% of neonatal mortality globally, resulting in a combined 1.7 million deaths each year [5]. Improved ability to monitor neonatal temperature could help improve outcomes for both preterm babies, who are at high risk of hypothermia, as well as babies with infections, who are at high risk of hyperthermia. In many low-resource settings, routine monitoring is simply not possible due to staff and equipment shortages. Our innovation, NTM, offers an affordable, rugged, low-power tool that provides constant monitoring with digital display of temperature and a simple light to notify a guardian or nurse when intervention is necessary. Furthermore, NTM is reusable, requires no consumables, and has a very simple design to facilitate easy maintenance and repairs.

This study is the first step in a systematic evaluation of NTM in comparison to the gold standard of electronic monitors used in high resource settings as well as two other alternatives specifically designed for low-resource settings: Thermospot and Bempu. Both are easy to use and can diagnose need for thermal care at a glance. Thermospot is a low-cost, one-time use disposable system that requires no power. Bempu is a $30 temperature monitoring bracelet that can run continuously for 30 days at which time it is replaced. A careful evaluation and comparison of these three solutions will provide critical data to support improved access to continuous temperature monitoring in low-resource settings. Future studies may evaluate not only the accuracy of these tools, but how they affect nurse/caregiver behavior and influence patient outcomes.

G. Objectives of the study

[i] Broad

The purpose of this study is to determine if three low-cost temperature monitoring devices can: 1) accurately measure neonatal temperature in a low-resource clinical setting, and 2) serve as an easy to use tool for monitoring temperature in low-resource settings.

[ii] Specific

The specific objectives for the current stage of this project are:

1. To determine the accuracy of the NTM, Bempu, and ThermoSpot devices when used by nurses in the neonatal ward by comparing
    a. Continuous temperature measurements
    b. Periodic temperature measurements
    c. Temperature during alarm events
2. To ensure the NTM is easy to understand and use in the
    a. Nursery with open cots, hot cots, and radiant warmers
    b. KMC ward

H. Methodology

[i] Study Type

This is a **pilot comparative study** to determine the level of agreement between three low cost temperature monitors against a continuous commercially available gold standard. The accuracy will be assessed both on infants in the neonatal ward as well as infants undergoing Kangaroo Mother Care (KMC).

[ii] 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 admitted to the neonatal or KMC wards.

[iii] Study Population

Subjects will be drawn from the population of infants being treated at QECH.

[iv] Study Period

We anticipate the study will take 2-3 months.

[v] Sample Size

This study will enroll up to 60 infants at Queen Elizabeth Central Hospital. Up to 30 subjects will be collected from the neonatal ward and 30 subjects from the KMC ward. This sample size will ensure that we are able to collect sufficient data from infants with a range of gestational ages, weights, temperatures, and treatment locations (ie open cot, radiant warmer). The data from this study can be used to calculate the sample size needed in a larger study to evaluate changes in outcomes and nurse behavior related to the different temperature monitors.

Inclusion criteria:

1. The subject is currently being treated at QECH in the neonatal or KMC ward.
2. Study devices are available for use.
3. The subject's caregiver has provided informed consent for their child to participate.

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.

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

Informed Consent:

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 and frequent monitoring may not be readily available. This study may benefit infants in the future as the accuracy and usability of the test devices can be used to improve access to temperature monitoring equipment in the future.

[vi] Data Collection

Training:

1. Prior to the start of the study, all study nurses/clinicians will receive training on how to use the test devices. Clinical decisions will still be based on the standard of care, which will not be interrupted during the study. The study nurse/clinician will apply the temperature sensors to the infant.
2. A research technician 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. 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.

Monitoring of Neonates:

During the trial, 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 three test temperature monitoring devices 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 gold standard as well as provide any other care needed.
3) A research assistant will use a laptop to collect data from the continuous temperature monitors (NTM and gold standard). The nurse will record the temperature readings every hour from all monitors on paper forms along with the standard of care.
4) Each time an alarm sounds from any device (Bempu and the commercial gold standard have audible alarms), the nurse will record all temperature values including a reading taken with the standard of care method. If the subject is found to be hyper/hypothermic, the nurse will respond with the appropriate standard of care.
5) Temperature monitoring will continue for up to 3 days. The research assistant may ask the nurse to remove and reapply the temperature probes during this period.

A research assistant will be available during the trial to mitigate any complications with the devices. If the subject's guardian, the nurse, or the research assistant indicates concern during the tests, temperature monitoring will be discontinued and the subject's treatment will return to the standard of care. The nurse can choose to remove one of the test devices and continue the study with the remaining monitors if any issue arises.

Clinical data will be collected on paper forms as is consistent with current clinical practice. Data from the temperature monitors 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.

The following section details the variables that will be measured or calculated in the study.

Intended Data Collection:

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. Additional temperature measurements taken as standard of care

2. Accuracy
    a. Recorded automatically by study equipment
        i. Abdominal temperature and alarms from Rice designed temperature monitor and gold standard device
    b. Recorded every hour by study nurse or as alarm events occur
        i. Temperature measurements from other devices
        ii. Temperature measurements using standard of care method (axillary)
        iii. Ambient temperature
        iv. Current thermal treatment, if any
    c. Movement/other caregiving
    d. Fit/tightness of the devices

A log of observed user error and comments may be used to improve the usability of the test devices.

[vii] 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 temperature sensors 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.

For the devices that do not provide a continuous numerical reading, the recorded state every hour will be compared to the gold standard at that point in time. The sensitivity and specificity for hypo/hyperthermia will be calculated for each device.

The ability of each device to accurately diagnose hypothermia will also be calculated with respect to the alarm events for each device for which they were recorded. The sensitivity and specificity will be determined using the number of false alarms collected during the study.

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

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] Results Presentation

Statistical analysis will be performed and means, limits of agreement, sensitivities and specificities will be reported. Tables and graphs may also be used to present any additional correlations, explain outliers, or demonstrate confounding effects.

[ix] Dissemination of Results

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.

I. Ethical considerations

The risks and discomfort associated with participating in this study are no greater than those associated with routine monitoring. No clinical decisions will be made on the basis of any test device. Infants will be removed from the study if study participation interferes with care. Infants at risk for hypothermia may benefit from close temperature monitoring provided by the test devices, commercial patient monitor, and dedicated study nurses. Others may benefit from this study in the future as this evaluation may help identify a low-cost, robust temperature monitor for low-resource hospitals.

The study protocol will be approved by COMREC and the Institutional Review Board at Rice University prior to initiation of the study. All investigators will be required to take the online *Protecting Human Research Participants* course provided by the NIH Office of Extramural Research. Any loss of patient data will be reported to the University of Malawi COMREC through the PI and to the Institutional Review Board at Rice University. Information will be de-identified to ensure patient confidentiality and data integrity.

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.

J. Possible Constraints

The subject may be removed from the study at any time at the request of the parents or clinicians. Axillary temperature measurements given as the standard of care will continue during the study and will not be interrupted.

After each subject, the devices will be cleaned thoroughly with a bleach solution.

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.

K. Study Requirements

The study will require the following:

Personnel:
Dr. Queen Dube, College of Medicine, Blantyre, Malawi: Principal Investigator
Research technician: A researcher from Rice University will travel to Blantyre (supported by Rice University).
Study nurse: Prince Mtenthaonga

Training:
Prior to the start of the study, all study nurses/clinicians will receive training on the use of the test devices by the Rice research team. Each member will pass a standard evaluation in order to operate the device. The Rice researcher and Dr. Dube will be available on site or by phone, email, and site visits to respond to any questions and/or concerns. The US- based investigators will be in frequent contact with the local team.

Paper: The Rice researcher will provide all consent and monitoring forms.

Equipment: The temperature monitoring devices will be provided by Rice for the study.

No transport, reagents, drugs or additional space will be required for the study.

L. Budget and budget justification

Salary Description	Cost
Queen Dube Honorarium	$1500
Study Nurse	$600
Printing Costs	$150
Direct Costs Total	$2250
10% F&A Costs	$225
Total	$2475

The test devices and paper forms (consents and monitoring forms) will be provided by Rice University. We have received funding from private donors to support this study.

This study is part of a larger plan to investigate and implement low cost temperature monitoring tools in neonatal wards. We estimate that this study comprises 30% of that work, for which an honorarium of $5000 was assigned. Therefore, we have listed the appropriate proportion of that honorarium here.

N. References

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