A. Title

Validation of a Low-Cost, Point-of-Care Bilirubin Measurement to Diagnose Neonatal Jaundice and Monitor Phototherapy in Hospitals in sub-Saharan Africa

B. Investigators

Principal Investigator: Dr. Queen Dube, College of Medicine, Blantyre, Malawi
Dr. Msandeni Chiume, Head of Department, Department of Paediatrics, Kamuzu Central Hospital, Lilongwe, 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

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Rice 360º: Institute for Global Health, Rice University, Houston TX

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Rice 360º: Institute for Global Health

Meaghan Bond
PhD, Dept. of Bioengineering, Rice University, Houston, TX, USA

Investigators' CVs: *(see Appendix 4)*

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

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

D. Executive summary

Type of Study:
This is a prospective study, the goal of which is to validate the accuracy of the BiliSpec device in measuring bilirubin levels in neonates relative to the laboratory spectrophotometric bilirubinometer and transcutaneous bilirubinometer measurements.

Problem:
Neonatal jaundice affects approximately 24 million newborns each year. If left untreated, severe jaundice can result in brain damage (kernicterus); while kernicterus is preventable, it is not treatable *(1)*. Severe jaundice may not present until several days after birth, thus early monitoring of serum bilirubin levels is critical, particularly in premature babies who are more likely to suffer from jaundice and who are at greater risk of death and disability due to jaundice. In high-resource settings, tools to measure serum bilirubin levels are readily available and have made neurological damage from jaundice exceedingly rare; these tools have proven too expensive and complex to implement widely in under-resourced settings *(2, 3)*. As a result, jaundice is diagnosed clinically in most low-resource settings using visual inspection of scleral yellowing; results are subjective and poor accuracy has been reported.

Recently, a team of researchers at Rice University in partnership with clinicians at Queen Elizabeth Central Hospital created BiliSpec, a low-cost battery-powered reader designed to immediately quantify serum bilirubin levels from a small drop of whole blood applied to a lateral flow strip. The simple and affordable BiliSpec system offers a faster and more cost-effective means to detect neonatal jaundice in under-resourced clinics and determine when phototherapy is needed. In 2017, a small 100 patient pilot study was performed at Queen Elizabeth Central Hospital in Blantyre, Malawi (Appendix 3). Results showed BiliSpec has comparable accuracy to laboratory standard and outperforms transcutaneous measurement of bilirubin *(4)*.

Objectives:
The purpose of this study is to validate the accuracy of BiliSpec in comparison to laboratory standard spectrophotometric and transcutaneous measurement of bilirubin levels in neonates at two central hospitals: Queen Elizabeth Central Hospital in Blantyre, Malawi and Kamuzu Central Hospital in Lilongwe, Malawi.

Methodology:
We will recruit up to 500 neonates at QECH and KCH each, for a total of up to 1000 neonates, at risk for jaundice based on clinical signs and symptoms or undergoing phototherapy for treatment

of jaundice. BiliSpec, laboratory standard spectrophotometric measurement, and transcutaneous measurement will be used to analyze bilirubin levels in both male and female babies with no preference towards a specific gender. Informed consent will be requested from the parents of all eligible babies on the ward for this study (Consent Forms in Appendix 1). If the guardian does not consent, the patient's bilirubin levels will be assessed using the standard of care on the ward. All eligible participants with consenting guardians will have their blood drawn via heel stick and measured with the three methods: BiliSpec, a commercially available spectrophotometric bilirubinometer according to standard laboratory practices, and a commercially available transcutaneous bilirubinometer. BiliSpec, the laboratory spectrophotometric bilirubinometer (Reichert UNISTAT® Bilirubinometer), the transcutaneous bilirubinometer, and accompanying equipment will be provided by the Rice study team. The Data Collection Form is found in the Appendix 2.)

Expected Findings:

We expect to find BiliSpec accurate and easy to use.

Dissemination:

The results of this study will be made available to the Ministry of Health, COMREC, the College of Medicine Library, the Department of Paediatrics at QECH and KCH, 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.

E. Literature Review and Background Information

Neonatal jaundice accounts for 114,000 infant deaths globally, with 85,500 of those deaths occurring in sub-Saharan Africa or South Asia. A further 180,000 neonates suffer permanent neurological damage every year from jaundice. Jaundice occurs when excess bilirubin builds up in the blood, and it is an especially common condition in premature babies, who lack sufficient liver function to excrete the excess bilirubin produced when fetal hemoglobin is broken down. Preterm babies also have a more permeable blood-brain barrier, which increases their risk of kernicterus by allowing unconjugated bilirubin easier access to brain tissue. Neonatal sepsis and Rhesus incompatibility also increase the risk of jaundice. Fortunately, the complications of neonatal jaundice can be prevented through the use of phototherapy which has been highly successful in well-resourced hospitals *(5)*. Bilirubin absorbs blue light, and phototherapy using blue light can be used to photodecompose bilirubin to a form that can be excreted. Laboratory determination of serum bilirubin concentration is vital in managing babies who are jaundiced. However, current methods of measuring total bilirubin are not feasible for district and health center laboratories. The standard for many hospitals is the diazo method for determining bilirubin levels in the patients. The diazo method requires many reagents, highly trained personnel, and a fully equipped laboratory to perform; all of which make implementation at the district level infeasible. Spectrophotometric determination of bilirubin requires no reagents, but requires both a centrifuge and a calibrated spectrophotometer, tools that cost thousands of dollars and are often not available in district hospital or health center laboratories. Transcutaneous measurement of bilirubin requires hardware and calibration consumables that are not affordable in many low-resource settings; accuracy of these devices is worse for neonates with dark skin and decreases during phototherapy *(3, 6, 7)*.

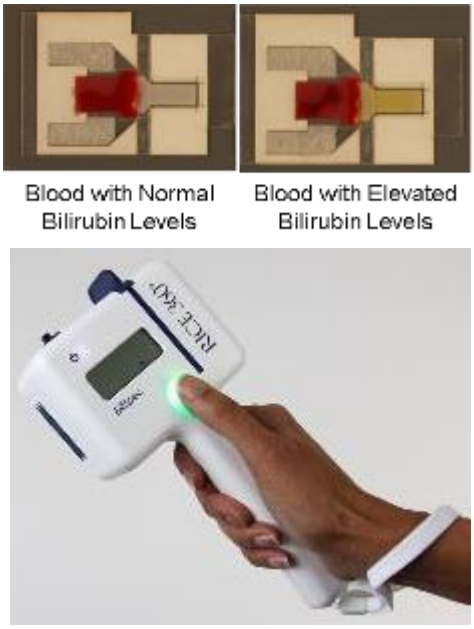


Figure 1. (a) Photograph of disposable lateral flow cards for blood collection. (b) BiliSpec Reader for measuring bilirubin

In response to this need for early bilirubin monitoring, researchers at Rice University created BiliSpec, a low-cost battery-powered reader designed to immediately quantify serum bilirubin levels from a small drop of whole blood applied to a lateral flow strip. BiliSpec has two components: (1) an inexpensive, disposable lateral-flow strip on which the clinician spots a drop of whole blood from a heel prick and (2) a battery powered reader which measures the light transmitted through the serum on the detection strip and displays a digital report of the bilirubin concentration (Figure 1).

BiliSpec has been evaluated in the laboratory and in a small pilot study (Appendix 3) at QECH to test efficacy and usability *(4)*. The BiliSpec lateral flow strip is capable of handling a range of blood volume to account for variations in volume from heel sticks. Full separation of plasma on the lateral flow strip takes approximately 1-2 minutes. In this time, the lateral flow device is sealed by the user after application of blood to prevent contamination or leaking. Measurement of bilirubin using BiliSpec during the pilot study yielded an average absolute difference of 0.8 mg/dL (95% CI of −1.7–2.2 mg/dL) as compared to the laboratory spectrophotometric measurement. The lateral flow strip costs less than $0.05 and we estimate the reader can be built for less $200 at low volume. We are optimizing BiliSpec to achieve a target accuracy of ±20% or 0.4mg/dL, whichever is greater (United States CLIA Standard) with a dynamic range up to 35 mg/dL, consistent with performance of bilirubin measurement techniques used in high-resource settings *(3)*. During the pilot study, 95% of samples were within CLIA guidelines, and simple changes are expected to improve performance. One limitation of the pilot study was the limited range of bilirubin concentrations tested; during the validation study, we will increase the number of neonates tested to increase the number of samples at high bilirubin concentrations. We believe that rapid adoption of this technology is possible since BiliSpec is affordable and simple to use at the bedside.

BiliSpec provides an important tool to monitor the efficacy and progress of phototherapy, ensuring appropriate treatment dosage and duration. Used together, BiliSpec and blue light phototherapy have the potential to reduce the morbidity and mortality associated with neonatal jaundice.

F. Rationale/Justification for the research project

Neonatal jaundice affects approximately 24 million newborns each year. Unfortunately, bilirubin monitoring systems used in the developed world are too expensive for low-resource settings; instead, nurses and doctors often must visually monitor babies to watch for possible development of jaundice based on yellowing of the sclera. This method has been shown to lack sufficient accuracy. Also, in this geographical setting, there are few pediatricians, and nurses often staff many babies at a time. The poor predictive ability of visual diagnosis and the high ratio of babies to nurses and doctors means that cases of jaundice are often not identified early enough, resulting in brain damage or death. This challenge is prevalent in district hospitals throughout Malawi. A more consistent, low-cost method of jaundice diagnosis and monitoring is needed. Based on the results of the pilot study, BiliSpec may meet this goal. It is now necessary to validate performance of the improved BiliSpec device in a larger population of neonates with a larger range of bilirubin concentrations.

G. Objectives of the study

[i] Broad

The objective of this work is to validate the accuracy and usability of a new point-of-care device called BiliSpec to measure bilirubin concentration in neonates in low-resource settings.

[ii] Specific

The specific aim of this study is to determine the accuracy of the BiliSpec device relative to a laboratory spectrophotometric bilirubinometer and transcutaneous bilirubinometer in the neonatal wards of Queen Elizabeth Central Hospital (QECH) and Kamuzu Central Hospital (KCH).

H. Methodology

[i] Study Type

This is a prospective study, the goal of which is to validate the accuracy of the BiliSpec device in measuring bilirubin levels in neonates relative to the laboratory spectrophotometric bilirubinometer and transcutaneous bilirubinometer measurements.

[ii] Place of Study

The clinical study will take place at QECH in Blantyre, Malawi and KCH in Lilongwe, Malawi. Patients will be recruited from the neonatal wards at QECH and KCH who are deemed to be at risk for jaundice or are undergoing blue light phototherapy to treat jaundice.

[iii] Study Population

Participants will be identified using the eligibility criteria stipulated below.

Inclusion Criteria:

1. The patient is currently being treated at QECH or KCH in the neonatal ward.
2. The patient is less than 28 days old (neonate).
3. The patient is deemed to be at risk for jaundice or the patient is undergoing blue light phototherapy for treatment of jaundice.
4. The patient's parent or guardian has provided informed consent for their child to participate.

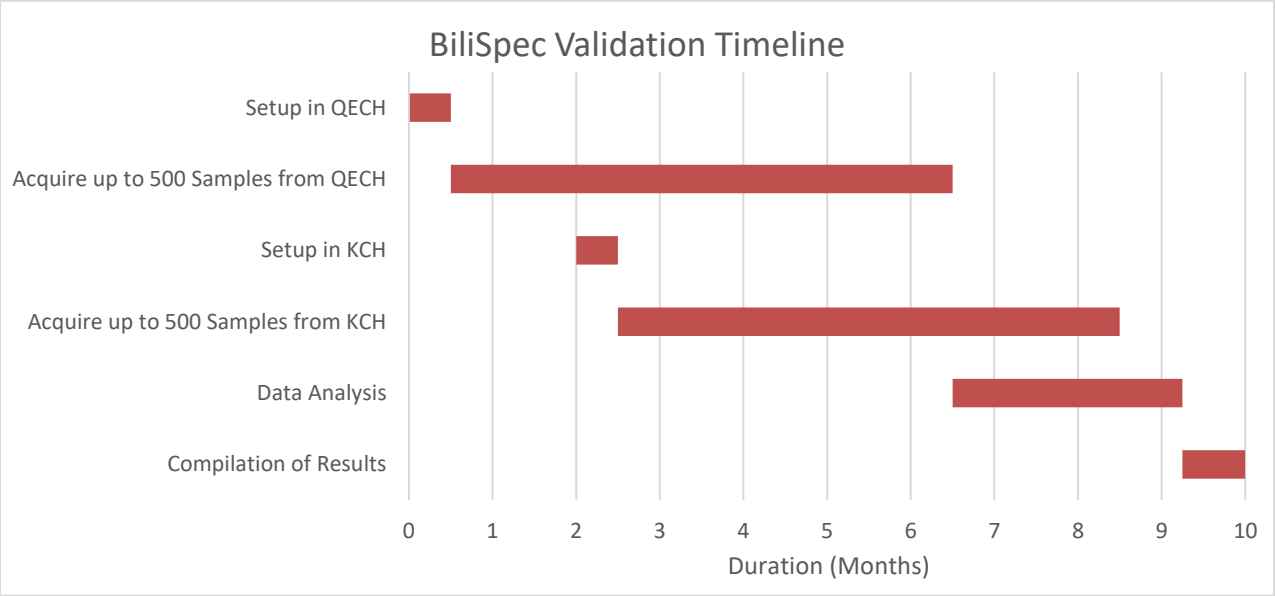
Exclusion Criteria:

1. Parent or guardian is unable or unwilling to provide informed consent.
2. The patient is unable to receive a blood draw/heel stick as determined by their clinician.

Families of neonates meeting eligibility criteria will be approached for consent to participate in the study by the investigator. If consent is not granted the patient will be treated with standard of care and will not participate in the study.

[iv] Study Period

See the below graphical representation and table of our anticipated timeline.



Task	Start Date (month)	Duration (Months)	End Date (month)
Setup in QECH	0	0.5	0.5
Acquire up to 500 Samples from QECH	0.5	6	6.5
Setup in KCH	2	0.5	2.5
Acquire up to 500 Samples from KCH	2.5	6	8.5
Data Analysis	6.5	2.75	9.25
Compilation of Results	9.25	0.75	10

[v] Sample Size

We will recruit a total of up to 1000 neonates at risk for jaundice based on clinical signs and symptoms.

During our pilot study, we evaluated 100 participants and collected 147 samples total. However only 7 samples collected were over 20 mg/dL. In addition to confirming the accuracy of BiliSpec in this validation study, we also want to ensure we have enough samples of clinically high bilirubin concentrations (>20mg/dL) to ensure our device functions properly over our intended dynamic range (0-35 mg/dL). To accomplish this, we will collect data from up to 500 participants at each location. Previous data have determined that the standard deviation of the difference between the Bilirubinometer and our device is 1.0 mg/dL. In order to detect a statistical difference between the Bilirubinometer and our device of 0.8 mg/dL, our target accuracy, at a statistical power of 90% and α of 0.05 using a paired test, we need 34 samples *(8)*. Since only 7 samples out of 100 participants during our pilot study were over 20 mg/dL, we will need up to 500

participants at each location to acquire the statistically significant number of samples over 20 mg/dL. The larger sample sizes will also us to conclusively validate the accuracy of the BiliSpec system over the full dynamic range of clinically relevant bilirubin concentrations.

In summary, 300 samples at each location are needed to show that the accuracy of BiliSpec is within 0.2 mg/dL of the laboratory standard spectrophotometric measurement (95% power, assuming 0.98 standard deviation of difference based on the pilot study); we have increased the number to up to 500 patients per location (1000 total) to increase the chances of recruiting patients over the full clinically encountered range of bilirubin concentrations, particularly at high concentrations.

This study will enroll up to 500 neonates at Queen Elizabeth Central Hospital and 500 neonates at Kamuzu Central Hospital who are deemed to be at risk for jaundice or who are receiving blue light phototherapy treatment for jaundice. We will compare the detection of bilirubin levels by BiliSpec to bilirubin monitoring with laboratory spectrophotometric bilirubinometry and transcutaneous bilirubinometry, the standard of care in developed settings.

[vi] Data Collection

Training

1. Prior to the start of the study, all study nurses/clinicians will receive training from a trained study engineer on BiliSpec and transcutaneous bilirubinometer use. Each member will pass a standard evaluation in order to operate the devices.
2. The local researchers will be available on site or 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.

Informed Consent

The investigator will provide details of the study to the guardians of all eligible subjects and will answer any questions. Guardians who consent to participation will be asked to sign a form documenting their consent (Consent Forms in Appendix 1) prior to the start of any study procedures.

Documentation of the consent process includes the following elements:

• Date 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.

The consent form will be updated or revised whenever important new safety information is available, whenever the protocol is amended, or whenever any new information becomes available that may affect participation in the study.

Enrollment

Enrollment will be after fully informed and written consent from the parent or guardian. Guardians will not be required in any way to have their child participate. If they choose not to participate, the care of their child will not be jeopardized. A parent will be free to withdraw their child from participating at any time, without explanation and such a decision will not affect standard of care. Each participant will be compensated 10USD (in local currency) per visit.

A participant identification number will be assigned. This number will be used for identification purposes throughout the study.

Bilirubin Testing of Neonates

The trained study nurse will assess the subject for clinical complications before performing the necessary heel prick blood draw.

- A transcutaneous measurement of bilirubin and a heel stick will be performed on the neonate by a trained study nurse or clinician.
- One drop of blood will be collected on the sample card and immediately used for analysis. BiliSpec will be operated by a trained nurse or trained research assistant.
- Another drop of blood, collected in a capillary tube, will be centrifuged and then measured using the laboratory spectrophotometric bilirubinometer (Reichert UNISTAT® Bilirubinometer 1310310C). The spectrophotometric bilirubinometer will be operated by trained research assistants from the Rice department of bioengineering and the University of Malawi. Bilirubin concentration values measured by the gold standard laboratory bilirubinometer will be used to guide diagnosis.

Measurements will be made at multiple time points as indicated clinically.

Data will be collected on paper forms (Appendix 2) as is consistent with current clinical practice. Clinical and/or research personnel will record information, excluding personal identifiers, on a standardized patient monitoring form. After the patient's participation is completed, a research assistant will collect and scan the form.

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

Variables/Time Points of Interest:

1. Baseline demographic and relevant medical information
    a. Date of Study
    b. Time of test
    c. Date of Birth
    d. Sex
    e. Weight
    f. Other comorbidities
    g. Start time of phototherapy (if applicable)
    h. Duration of phototherapy at time of measurement (if applicable)

2. Accuracy
    a. Bilirubin levels as measured by BiliSpec using blood drawn from a heel stick.
    b. Bilirubin levels as measured by laboratory spectrophotometric determination which will be used as the gold standard for determining bilirubin concentration and validating the BiliSpec system.
    c. Bilirubin levels as determined by transcutaneous measurement.

[vii] Data Analysis

We will determine the neonatal bilirubin concentration in mg/dL using the BiliSpec device, the gold standard laboratory spectrophotometric bilirubinometer, and the transcutaneous bilirubinometer described in the testing procedure. Measurements of bilirubin levels will be compared. All data will be recorded using the data collection form (Appendix 2). We will also analyze the usability and robustness of BiliSpec with regards to usability and device function by maintaining a log of any user error in using the device and a log of any observed device malfunctions. Data will also be collected on the effectiveness of BiliSpec to monitor neonates undergoing phototherapy.

Personal identifiers will be removed and confidentiality of the subjects will be strictly preserved. The data will be kept on a secure server accessible only to the study personnel.

The research team from Rice University, QECH, and KCH will be responsible for all data analysis. Data will be entered and stored in a database that will export to a CSV file. We plan to analyze data using Excel and Matlab and associated statistics packages.

[viii] Results Presentation

We will validate the accuracy and usability of Bilispec in comparison to laboratory spectrophotometric measurement and transcutaneous measurement during use in a low-resource hospital. A research manuscript will be prepared describing the device in detail and the

results of the study.

[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 at QECH and KCH, 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 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 risks and discomfort associated with participation in this study are no greater than those ordinarily encountered in daily life or during a routine pediatric checkup. The BiliSpec device is

exempt from the US Investigational Device Exemption (IDE) requirements as it meets the exemptions outlined in 21 CFR §812.2(c)(3).

Potential Benefits and Compensation of the Proposed Research to Human Subjects and Others:
Neonates and infants at risk for jaundice may benefit from participating in this study as alternative forms of accurate monitoring may not be readily available. This study may benefit neonates in the future as BiliSpec may enable cost-effective, accurate detection bilirubin levels in neonates at risk for jaundice. In addition, each participant will be compensated 10USD (in local currency) per visit.

K. Study Requirements

The study will require the following:

Personnel:
Dr. Queen Dube, College of Medicine, Blantyre, Malawi: Principal Investigator
Dr. Msandeni Chiume, Head of Department, Department of Paediatrics, Kamuzu Central Hospital, Lilongwe, Malawi: Principal Investigator
Technical Engineer: An engineer from Rice University will travel to Blantyre (supported by Rice University).
Study Nurse: Malawian nurse supported by Rice University to obtain consent and operate BiliSpec.

Training: Prior to the start of the study, all study nurses/clinicians will receive training on BiliSpec and the transcutaneous bilirubinometer use by the Rice research team. Each member will pass a standard evaluation in order to operate the device. The Rice researcher and Dr. Dube at QECH or Dr. Chiume at KCH 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 bring all forms from Houston, Texas to Blantyre, Malawi and Lilongwe, Malawi.

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

L. Budget and budget justification

Salary Description	Cost (MK)	Cost (USD)	Quantity	Cost (MK)	Cost (USD)
Paediatrician Salary, QECH	7,200,000	$10,000	1	7,200,000	$10,000
Paediatrician Salary, KCH	7,200,000	$10,000	1	7,200,000	$10,000
Clinician Salary	4,320,000	$6,000	1	4,320,000	$6,000
Nurse Technician Salary	3,024,000	$4,200	1	3,024,000	$4,200

Supplies					
Gloves	3,500	$4.86	10	35,000	$30
Cotton Roll	9,500	$13.19	5	47,500	$80
Lancets	3,800	$5.28	20	76,000	$32
Spirit Swabs	2,200	$3.06	20	44,000	$20
Plaster	1,900	$2.64	50	95,000	$16
Participant Compensation					
Participant Compensation	7,200	$10	1000	7,200,000	$10,000
Direct Costs Subtotal				**29,241,500**	**$40,378**
10% F&A Costs				2,924,150	$4,038
COMREC Fee				108,000	$150
Total				**32,273,650**	**$44,566**

The BiliSpec devices, laboratory spectrophotometric bilirubinometry devices, transcutaneous bilirubinometery devices, and paper forms (consents and monitoring forms) will be provided by Rice University. We have received funding from USAID's Saving Lives at Birth program to support this study which provides for a subcontract to COM that includes the 10% F&A costs.

N. References

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Appendix 2 – Data Collection Form

Protocol Title: Validation of a Low-Cost, Point-of-Care Bilirubin Measurement to Diagnose Neonatal Jaundice and Monitor Phototherapy in Hospitals in sub-Saharan Africa.

Record subject # on consent

Subject #_____ **Date**_____
COMREC Protocol #_____ Rice Protocol # _____
Protocol Expiration _____ Protocol Expiration _____
Patient #_____of 1000 Max Accrual Patient #_____of 1000 Max Accrual

NO CLINICAL WORK SHOULD PROCEED WITHOUT FIRST COMPLETING THE ENTIRE SECTION ABOVE!!!

DOB: _____ Gender: M F **Consent signed:** YES NO
Birth Weight (kg): _____
Phototherapy Start date (dd/mm/yy): _____

Bilirubin results:

	Date (d/m/y)	Time (24hr)	BiliSpec (mg/dL)	Transcu-taneous (mg/dL)	Bilirubin-ometer (mg/dL)	Phthrpy (y/n)	Notes
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							

Comorbidities: _____

Codes for notes (indicate in notes above if occurs):

1. Difficult blood collection
2. Collection pad not visibly filled
3. Visible lysis on strip
4. Visible lysis in laboratory standard sample
5. Device Error: _____ Sample#(s):_____

Other Patient Notes: _____