BILICAM CLINICAL VALIDATION STUDY

INVESTIGATIONAL PLAN

Version 2.0

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BILICAM CLINICAL VALIDATION STUDY
INVESTIGATIONAL PLAN

A. PURPOSE

A clinical validation study will be conducted on the BiliCam system, a non-invasive technology to estimate total serum bilirubin (TSB) levels in newborn infants. The technology is based on analysis of digital images obtained using the BiliCam app installed on a commodity smartphone. The purpose of the clinical validation study is to demonstrate that the accuracy of BiliCam in estimating TSB levels in newborn infants is similar to the accuracy of the predicate device, the JM-103 (Draeger Medical, Telford, PA) brand of transcutaneous bilirubinometer. The primary study outcome is the correlation between paired TSB and Bilicam-estimated (BCB) values among a racially and ethnically diverse sample of newborn infants. The performance goal for demonstrating that BiliCam has similar accuracy as the JM-103 is:

The lower limit of the 95% confidence interval (95% CI) around the calculated correlation coefficient (r) will be $\geq$ 0.83.

This performance goal is based on the results of studies of JM-103 used to support 510(k) applications for this device (K021622, K042522). In these studies, correlations between paired JM-103 and TSB measurements ranged from 0.84 to 0.946.[1,2]

Data for the clinical validation study will be collected using the BiliCam app installed on iPhone 5s smartphones. In addition, if feasible, image data on study participants will also be collected using the BiliCam app installed on iPhone 7 phones. The data obtained with the iPhone 7 phones will be used for algorithm development and testing. Note that no BCB value will be returned to the iPhone 7 during this study as the data is being collected for research and development purposes.

B. PROTOCOL

B-1.0 Scientific rationale

Neonatal jaundice is an almost ubiquitous condition. It is estimated that 60-84% of newborns develop visual jaundice in the first few days of life.[3,4] Systematic assessment to identify newborns with significant hyperbilirubinemia is a central focus of care during the birth hospitalization in the US. In a study conducted by the Better Outcomes through Research for Newborns (BORN) network, respondents from 86% of 60 newborn nurseries across the US reported that they screened virtually all neonates with either a transcutaneous bilirubin (TcB) or TSB measurement prior to discharge.[5] Since TSB levels are the "gold standard," and used to determine clinical care, there are advantages in using TSB screening in newborn nurseries. TcB measurement is a non-invasive technology to screen newborns for jaundice using a hand-held portable device.[6] Although not as accurate as TSB measurement, there are several validated decision rules for using TcB measurements to determine which newborns need a blood draw for a TSB level; use of TcB screening and these screening rules can obviate the need for a blood draw in 80% - 90% of neonates during their birth hospitalization.[6-8] TcB measurement also has an advantage in that, because it is a portable and non-invasive methodology, it is easy to perform serial measurements on an infant and the results are virtually instantaneous.[5] Thus, either TSB or TcB screening is an effective method to identify jaundiced newborns during their newborn nursery stay.

Unfortunately, bilirubin levels typically peak in neonates around 96 hours of life, well after most infants are discharged from the newborn nursery.[6,9-13] Because of this, the American Academy of Pediatrics (AAP)

recommends that newborns discharged before 72 hours of age be seen by a healthcare provider within the subsequent 48-72 hours to assess for jaundice.[6,10 14] However, accurate assessment of the severity of jaundice in outpatient neonates is problematic. TSB measurement is more difficult in newborns after discharge than it is during the birth hospitalization.[6] TcB measurement would be a viable option, however, TcB meters are not in wide use in outpatient settings, likely because each TcB meter costs thousands of dollars.[4,6] Given these obstacles, the outpatient assessment of jaundice in neonates is generally done by visual inspection of an infant's skin to assess the degree of yellowness.[4] However, while both parents and clinicians are usually able to identify the presence of jaundice, there is ample evidence that even experienced healthcare providers cannot accurately estimate its severity.[4] In studies comparing visual assessment of jaundice with TSB levels, correlation coefficients are in the 0.36 - 0.75 range, with poor inter-observer agreement.[4,15-20] Most concerning are data that indicate that, when using visual assessment, clinicians frequently underestimate the severity of jaundice.[4,15]

In resource-poor areas, kernicterus continues to be a major, and underappreciated, source of neonatal morbidity and mortality. There are ~500,000 newborns each year born in low- and middle-income countries who develop "extreme hyperbilirubinema" (EHB) leading to 114,000 neonatal deaths and 75,000 cases of kernicterus.[21] A primary reason for these depressing statistics is the lack of ability to measure bilirubin levels in many locations, particularly now that low-cost phototherapy units have been developed.[22,23]

There is clearly a global need for an inexpensive and widely available technology that could be used by physicians, nurses, other healthcare workers and parents to screen newborns for jaundice. Based on this need, a group of faculty and staff from the University of Washington developed BiliCam, a technology based on the analysis of digital images obtained with a smartphone app to provide an estimate of TSB.[24]

A detailed description of BiliCam is provided in section D. Briefly, the BiliCam app is designed to obtain images of a portion of a newborn's skin in a standardized manner using a commodity smartphone and transmit the image data via the internet to a computer server for analysis. The process of obtaining a set of Bilicam images is initiated by placing a color calibration card (a modified Macbeth Color Checker in the shape of a hollow square) on the newborn's sternum.[25] This card helps to both account for variations in lighting conditions and facilitate image capture and data extraction. The user starts the app and a red square appears on the smartphone screen. When this square is properly aligned with the color calibration card and lighting is adequate, the app automatically captures images using the smartphone camera; both a flash and ambient lighting image are obtained. The square of the viewfinder becomes smaller directing the user to move further from the newborn and the process is repeated. Ultimately, a set of 6 images, both flash and non-flash images at each of 3 distances from the newborn, are obtained. The user then "submits" the images to a cloud-based server.

At the server, the red, green and blue (RGB) values of pixels from multiple regions of the color calibration card and from an area of the newborn's skin in the "hollow" portion of the card are measured; these measurements are also transformed into additional color spaces. A set of these color measurement values, or "features", are entered into an algorithm used to calculate a bilirubin value. This estimated bilirubin level is then transmitted back to the smartphone.

B-1.1 Preliminary study

Between October 2014 and July 2016 a preliminary study of BiliCam was conducted. The goals of the preliminary study were two-fold: 1) estimate the accuracy of BiliCam in estimating bilirubin levels in a racially and ethnically diverse sample of newborns, and 2) develop a specific algorithm for converting image data into the estimated bilirubin level. For the study, data on paired TSB values and BiliCam-estimated bilirubin levels

were collected on a racially and ethnically diverse sample of 530 newborns from 7 institutions across the US using the BiliCam app installed on an iPhone 5s. Data were collected on newborns both during their birth hospitalization and in outpatient settings. TSB values ranged from 0.6 mg/dL to 24.8 mg/dL.

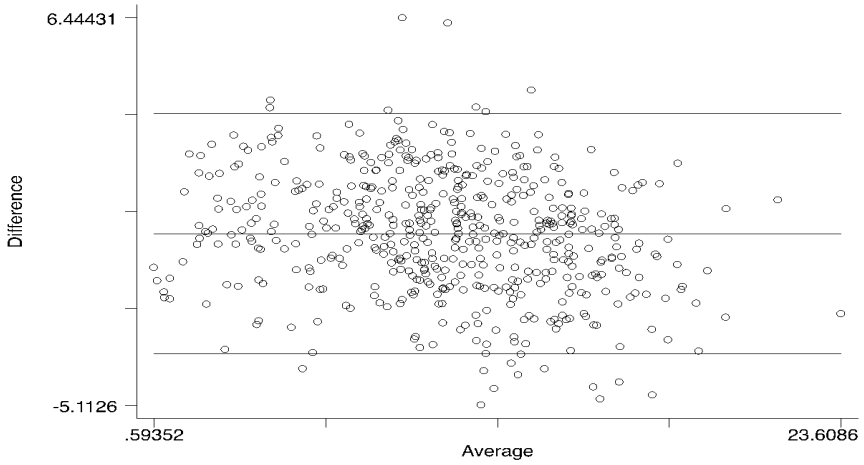
Using a 10-fold cross validation procedure to provide an unbiased assessment of accuracy, the correlation between estimated bilirubin levels and the matching TSB value was 0.91 (95% confidence interval [95% CI] 0.89, 0.92). As summarized in the table below, BiliCam worked well in newborns with a variety of skin pigmentation.

Table. Correlation between BiliCam-estimated bilirubin (BCB) levels and TSB levels in newborns from different racial and ethnic groups.

Group	Number	Correlation coefficient
All	530	0.91
White	293	0.92
African American/Black	110	0.90
Asian	112	0.88
Hispanic/Latino ethnicity	139	0.91

The mean difference between the estimated bilirubin level and TSB was 0.01 mg/dL $\pm$ 1.8 mg/dL, with a range of -.5.1 mg/dL to +6.4 mg/dL. A Bland-Altman plot summarizing the differences between BCB and TSB is shown below; the limits of agreement were -3.6 mg/dL to +3.6 mg/dL.

Figure. Bland-Altman plot of differences between BiliCam-estimated bilirubin (BCB) levels and TSB levels.



TcB measurements were made on a subgroup of 331 study newborns. In these infants the correlation between TcB and TSB was 0.91 (95% CI 0.90, 0.93). The mean TcB-TSB difference was 0.51 mg/dL $\pm$ 1.8 mg/dL, with a range of -4.6 mg/dL to +5.9 mg/dL; the limits of agreement were -3.2 mg/dL to +4.2 mg/dL.

The results from this study suggest that BiliCam has comparable accuracy to TcB, both from the data collected on TcB measurements in the project and in other published studies. In previous studies, the correlation coefficients between TcB and TSB have ranged from 0.77 – 0.93.[4] In a study that included data on 925 matched TcB and TSB levels in babies at 27 newborn nurseries across the US, the mean TcB – TSB difference was 0.84 mg/dL ± 1.78 mg/dL, and the range of differences was -6.9 mg/dL to 8.8 mg/dL. The correlation between paired measurements was 0.78.[5]

In addition to assessing the accuracy of BiliCam, the study data were used to develop a "locked down" algorithm for converting image data into an estimated bilirubin level. The algorithm resides on the server, where the estimated bilirubin level is determined. This estimated level is then transmitted via the internet back to BiliCam app on the user's smartphone.

Overall, BiliCam has the potential to revolutionize the management of neonatal jaundice. During the birth hospitalization, BiliCam could provide a less expensive and more widely available technology to screen newborns for hyperbilirubinemia. For clinicians (physicians, nurses, nurse midwives, lactation consultants) in outpatient settings, BiliCam could be an effective tool for determining which newborns require a blood draw for a TSB level. In addition, because of its low cost and wide availability, in low- and middle-income countries BiliCam might become part of a system of care that could save thousands of lives annually be identifying jaundiced newborns before they develop kernicterus and prevent significant morbidity from EHB.

B-2.0 Study procedures

A prospective study will be conducted at a minimum of 3 sites comparing paired TSB and BiliCam-estimated bilirubin (BCB) levels in a racially and ethnically diverse sample of newborn infants.

Inclusion criteria

- Age < 192 hours
- Born at ≥ 35 weeks gestation
- Parent provides written informed consent for child to participate
- Parent speaks and reads English

Exclusion criteria

- Previous or ongoing treatment with phototherapy for hyperbilirubinemia
- Medical or other complications that preclude completion of the study as determined by the principal investigator at each study site

B-2.1. Sample size

It is planned to have 225 subjects complete study procedures, defined as having blood drawn for a TSB level and valid BiliCam images obtained, with the goal of collecting data on ≥ 200 newborns who have paired BCB and TSB data available for the primary analyses. As described in section B-2.2, at each study site, one of two enrollment plans will be used: "Simultaneous" (in which enrollment and the study visit will occur at one time-point), or "Staged" (in which the study visit occurs at a later time from enrollment). At sites using the Staged enrollment plan, a proportion of subjects who are enrolled will not complete study procedures because: 1) they

become ineligible because of the occurrence of an exclusion criterion after enrollment, but before the study visit occurs, 2) parents withdraw consent, or 3) subject does not return for the study visit. At these sites, up to 150 subjects will be enrolled and enrollment will be discontinued when a maximum of 75 newborns at the site have completed study procedures. At sites using the Simultaneous enrollment plan, because all subjects are expected to have completed study procedures, up to a maximum of 75 subjects will be enrolled.

B-2.2. Enrollment plan

The goal of the enrollment plan is to obtain data on newborns across the entire measuring range of BiliCam (0-20 mg/dL) while oversampling newborns with high TSB levels. The use of two enrollment plans will enable this distribution. At sites using the Simultaneous enrollment plan, newborns will be enrolled at the time (within 2 hours) that blood is being obtained for a TSB level because the newborn is clinically jaundiced (i.e. the TSB is being ordered for clinical purposes). Thus, enrollment and the study visit will occur simultaneously. At Staged enrollment plan sites, subjects will be enrolled prior to being 48 hours old; these subjects will have a study visit after they are 48 hours old (i.e. the enrollment and the study visit will occur at different times). For these subjects, blood will be obtained for a TSB level as part of the study at the study visit.

A subject will be considered to be enrolled in the study once the consent is signed by his/her parent. Once enrolled, a subject's participation will be documented on the study case report forms and the subject will be included in the analyses of study data.

Enrollment procedures are described in detail below.

B-2.2.1- Simultaneous enrollment plan procedures

Subjects who are age-eligible and are either inpatients or being seen for outpatient visit (by a lactation consultant or other provider) are eligible for enrollment. On a daily basis, the site research assistant will review the medical records of healthy newborns who are hospitalized for routine post-birth care. The research assistant will identify those newborns who meet inclusion and exclusion criteria, and who have had blood drawn within the previous 2 hours or have an order for a blood draw for a TSB level. The research assistant will approach the parent(s) of an eligible hospitalized newborn after discussion with a healthcare provider (e.g. nurse) who is caring for the newborn to ensure that it is a good time to approach the family (e.g., the mother is stable medically, not sleeping, etc). The research assistant will discuss the study with the parent(s) of an eligible newborn and, if the parent(s) is interested in participating, have the parent(s) read and sign the informed consent form.

At the time that the parent signs the informed consent form, a new study file will be opened.
Each file has a unique study ID number assigned. The research assistant will record the subject's medical record number next to the assigned study ID number on the **Site Enrollment Log.** The research assistant will also record the date that the informed consent form was signed. The signed consent form will be put in the appropriate study file. (The **Site Enrollment Log** and study case report forms are included in appendix 1).

After the consent form has been signed, the research assistant will ask the parent(s) to complete the **Parent Enrollment Form**, providing the sex, race and ethnicity of the newborn. (The **Parent Enrollment Form** is included in appendix 1). The research assistant will also obtain the enrolled subject's date and time of birth form the subject's medical record. The research assistant will complete the **Subject Enrollment Case Report Form,** which includes the subject's, sex, race and ethnicity (abstracted from the **Parent Enrollment Form**), and date and time of birth. In addition, the research assistant will confirm on the **Subject Enrollment Case Report Form** that the subject was born at $\geq$ 35 weeks gestation (based on review of the subject's medical record) by checking the appropriate box on the form.

Age-eligible newborns being seen for outpatient follow-up are also eligible for enrollment. On a daily basis the research assistant will review the list of newborns being seen by a lactation consultant or other provider. The research assistant will identify newborns who meet inclusion/exclusion criteria and who have either had blood obtained for a TSB level < 2 hours previously or have an order to have blood drawn for a TSB level because of clinical jaundice. After discussion with the provider to ensure that an identified newborn is suitable for enrollment, the research assistant will discuss the study with the parent(s) of the eligible newborn and, if the parent(s) is interested in participating, have the parent(s) read and sign the informed consent form. The research assistant will complete the **Site Enrollment Log,** have the parent(s) complete the **Parent Enrollment Form**, and complete the **Subject Enrollment Case Report Form** as described above.

B-2.2.2 Staged enrollment plan procedures

On a daily basis, the site research assistant will review the list of newborns who are hospitalized for routine post-birth care and identify those neonates who are potentially eligible for the study. The research assistant will approach the parent(s) of an eligible hospitalized newborn after discussion with a healthcare provider (e.g. nurse) who is caring for the newborn to ensure that it is a good time to approach the family (e.g., the mother is stable medically, not sleeping, etc). The research assistant will discuss the study with the parent(s) of an eligible newborn and, if the parent(s) is interested in participating, have the parent(s) read and sign the informed consent form.

At the time that the parent signs the informed consent form, a new study file will be opened.
Each file has a unique study ID number assigned. The research assistant will record the subject's medical record number next to the assigned study ID number on the **Site Enrollment Log.** The research assistant will also record the date that the informed consent was signed. The signed consent form will be put in the appropriate study file.

After the consent form has been signed, the research assistant will ask the parent(s) to complete the **Parent Enrollment Form**, providing the sex, race and ethnicity of the newborn. The research assistant will also obtain the enrolled subject's date and time of birth from the subject's medical record. The research assistant will complete the **Subject Enrollment Case Report Form,** which includes the subject's sex, race and ethnicity (abstracted from the **Parent Enrollment Form**), and date and time of birth. In addition, the research assistant will confirm on the **Subject Enrollment Case Report Form** that the subject was born at $\geq$ 35 weeks gestation (based on review of the subject's medical record) by checking the appropriate box on the form

At enrollment, the research assistant will explain the timing for the study visit with the parent(s). Prior to hospital discharge, the research assistant will schedule the study visit with the parent(s) for when an enrolled newborn is 2-6 days old. If possible, the study visit will be scheduled at the same time as a clinical visit for the enrolled subject.

B-2.3. Procedures for the study visit

Study visits will occur simultaneously with enrollment at sites using the Simultaneous enrollment plan and at a later time for subjects enrolled at sites using the Staged enrollment plan. At the beginning of the study visit at all sites, the research assistant will confirm on the **Study Visit Case Report Form** that the subject does not have any exclusions for participation. Specifically, the research assistant will check the appropriate boxes on the CRF to verify that the subject: 1) is <192 hours old, 2) has not received phototherapy for treatment of hyperbilirubinemia, and 3) that the patient has not been excluded by the site PI. After confirming that the subject is eligible, the research assistant will obtain a series of images using the BiliCam app installed on the iPhone 5s assigned to the study.

Once the research assistant has obtained image data on a study participant using the BiliCam app installed on the iPhone 5s, additional image data (the same series of images) will be obtained using the BiliCam app installed on the iPhone 7 assigned to the study, if possible. At the discretion of the research assistant, these additional images may not be acquired if not practically possible (e.g. the newborn has become too fussy). The procedures for obtaining the images with the iPhone 5s and iPhone 7 are provided in Appendix 2.

B- 2.3.1 Procedures for obtaining TSB values for subjects

At sites using the Staged enrollment plan, blood will be obtained by a qualified phlebotomist on study subjects immediately before, or after, the images for the BCB are obtained (i.e. within 2 hours) and sent for assay by the clinical laboratory at each site. At these sites, some study visits will occur at the time of a clinical visit. If the clinicians evaluating the baby at the clinical visit (occurring simultaneously with the study visit) determine that a TSB level is needed for clinical purposes, a second blood sample for the study will not be obtained; the TSB level obtained for clinical purposes will be used as the study value. No blood will be obtained for study purposes at sites using the Simultaneous enrollment plan. At these sites, BiliCam images will be obtained at the time (within 2 hours) of a blood draw for a TSB level that is being obtained for clinical purposes.

B -2.3.2. Completing the Study Visit Case Report Form

After obtaining the BCB result on the mobile phone assigned to the study, the research assistant will record the value, and the date and time that the images were obtained, on the **Study Visit Case Report Form.** If a BCB value was not obtained, the research assistant will record "N/A" for the result, and indicate the reason why the BCB value was not available. Possible reasons for not obtaining a BCB value include not obtaining all needed images, issues with lighting, no value downloaded to phone after images are submitted to the server, or a value reported as ">20.0," i.e. outside of measuring range of the device. The initials of the research staff who performed the BiliCam test will be recorded on the CRF.

The calibration card used for the BiliCam test will be affixed to page 2 of the **Study Visit Case Report Form** in the spot indicated on the form.

At the time that the "study" TSB level result is available from the clinical laboratory at each site on a study subject, the level (in mg/dL) will be recorded on the **Study Visit Case Report Form**. In addition, the date and time that the blood was reported as being obtained will also be recorded on the CRF. For subjects in whom the "study" TSB level is a value that was obtained for clinical purposes (including all subjects from Simultaneous enrollment plan sites and a portion of subjects at sites using the Staged enrollment plan), if more than one valid level was obtained within 2 hours of the time that the BiliCam images are obtained, the TSB level drawn closest to the time that the BiliCam images were obtained will be selected as the "study" value. On the **Study Visit Case Report Form** the research assistant will indicate whether the listed TSB value was obtained specifically for the study or for clinical purposes. If no valid TSB level is available, the research assistant will record "N/A" for the result and indicate the reason on the form. Possible reasons include a blood sample that was too hemolyzed for analysis, an inadequate sample (i.e. quantity of blood not sufficient for the assay), and parents declining a study blood draw.

Research staff will document on the **Site Enrollment Log** when the **Study Visit Case Report Form** was completed on each subject by recording the date in the appropriate box on the log for the appropriate Study ID number. If the subject does not have a study visit (i.e. the subject's parent(s) withdraws consent prior to the visit, the subject is excluded by the site principal investigator, the subject is excluded because of phototherapy, the subject is lost to follow-up, or another reason), "N/A" will be recorded in the appropriate box on the **Site**

Enrollment Log.

B-2.3.3. Completing the iPhone 7 Case Report Form

In addition to the **Study Visit Case Report Form** on each subject, the research assistant will also note if additional image data were obtained on the study participant using the BiliCam app installed on the iPhone 7 using the **iPhone 7 Image Collection Case Report Form** (appendix 1). If image data were obtained, the research assistant will check the "yes" box on the CRF. If no images with the iPhone 7 were obtained, the research assistant will indicate the reason on the CRF. Possible reasons include, "No, participant too fussy," "No, parents declined," or "No, problem with phone/app." Note that no BCB value will be returned to the iPhone 7 during this study.

B-2.3.3. Documenting adverse events

Because of the minimal risk nature of the study, it is anticipated that adverse events to subjects related to use of the BiliCam device will be infrequent and, if they occur, mild in severity. If an adverse event occurs for a subject during use of the BiliCam device (study mobile phone, BiliCam app, color calibration card) or during the study blood draw (Staged enrollment plan sites only) it will be documented on the **Adverse Event Case Report Form** (appendix 1). On the CRF, research staff will provide a narrative of the event, the site PI will determine the relationship to the device and this determination will be recorded on the form using the following guidelines:[26]

- **Likely Related**: An adverse event that follows a reasonable temporal sequence from use of BiliCam with the subject, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- **Possibly Related***:* An adverse event that follows a reasonable temporal sequence following the use of BiliCam with a subject, but that could readily have been produced by a number of other factors.

- **Not related***:* The adverse event is clearly not related to use of BiliCam with a subject. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

The date of resolution of the adverse event will be noted on the CRF along with a narrative description of the outcome. The severity of the adverse event will also be categorized on the CRF using the following guidelines:[26]

- **Mild:** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate:** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- **Severe:** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

The research staff will also classify each adverse event as serious or not. An adverse event will be classified as serious if it: results in death, is life-threatening, requires hospitalization, results in significant or permanent disability, causes birth defects or may require medical or surgical intervention to prevent one of these outcomes. Completed **Adverse Event Case Report Forms** will be reviewed and signed by the site principal investigator. The study monitor will be notified as soon as possible whenever an Adverse Event Case Report Form is completed. The study monitor will notify the sponsor in any case in which an unanticipated adverse device event occurs.

B-2.3.4. Modifying the app

No modifications to the app impacting clinical function are anticipated during the study. If modifications of the app are made during the study, all site investigators will be notified and the changes will be evaluated and accounted for in the analysis of study data.

B-2.4. Procedures for use of additional study forms

Site Principal Investigator Exclusion Explanation Form— The site principal investigator may exclude enrolled subjects from completion of the study for medical, or other reasons. Examples include: a subject develops medical complications after enrollment that precludes study completion, or Child Protection/Child Welfare Services assume custody of a subject prior to study completion. If the site principal investigator determines that a subject should be excluded from the study after enrollment, this form will be completed to briefly explain the decision. (Copy of form included in appendix 1).

BiliCam Incident Report Form-- This form will be completed whenever there is an issue with the BiliCam app installed on a mobile phone assigned to the study. Listed issues include: app closing ("crashing") while preparing to obtain images, while obtaining images or while trying to submit images; inability to submit images; problems with "auto capture" of images, failure in receiving BCB level, issues with lighting, and others. The form will be completed by the research staff individual who experienced the issue and will also include comments. Note: This form will not be included in the study file for individual subjects, but completed on an ad hoc basis. (Copy of form included in appendix 1). Completed forms will be sent to the study monitor.

Protocol Deviation and Other Problems Report Form—This form should be completed when there is a deviation from the approved protocol; examples might include consenting issues, inadvertently enrolling ineligible participants, or collecting data on a participant outside of the approved age. Other problems might include: losing study phones or having them stolen, inadvertent disclosure of study data or losing study data.

When completing the form, no identifying information about a participant should be included. The research assistant or site principal investigator should record the date when the form was completed and the site. If the event involves one specific participant, the participant's study ID should be listed on the form. If multiple participants are involved, record "N/A" for participant study ID and list the study ID numbers in the narrative section of the form. If no specific participant was involved in the event, record "N/A" for study ID.

The form consists of three narrative sections. For the first part, a description of the actual protocol deviation or other issue should be provided. In the second part of the report form, the factors that led to the event occurring (i.e. why the protocol deviation or other issue happened) should be described. In the final narrative section, actions taken to ensure that the event will not recur should be described.

When a protocol deviation or other issue occurs, it should be noted on the form whether the problem affected any subject's rights, safety or well-being and/or if the scientific integrity of the investigation was afftected. If the answer to this item on the form is "yes," the site IRB should be notified.

Once the form has been completed, it should be signed and dated by the site principal investigator. The study monitor should be notified as soon as possible if a protocol deviation or other problem that warrants completion of the **Protocol Deviation and Other Issues Report Form** occurs. The completed form will be provided to the study monitor. In addition, as needed, the site IRB should be notified about the event.

"Note to file" form-- An additional form will be included in the study file for each subject that is to be completed as needed when unusual events or problems occur. This form will also be used to provide explanations when a subject does not complete the study, unless the explanation is provided elsewhere (e.g. in the **Site Principal Investigator Exclusion Explanation Form**). (Copy of form included in appendix 1).

B-2.5. Completion of Study Exit Case Report Form

The **Study Exit Case Report Form** will be completed for every enrolled subject when his/her participation has ceased. (Copy of form included in appendix 1). The form is used to document the final outcome for the subject; the research assistant will indicate the outcome on the form. Possible outcomes include:

- Completed study: Indicating that the subject completed the study visit, defined as having BiliCam images obtained and blood drawn for a TSB level.
- Parent(s) withdrew consent: Indicating that the parent(s) of a subject changed their mind about participating in the study at any point prior to completion
- Subject lost to follow-up: Indicating that the subject did not return for the study visit and no explanation was provided by the parent(s).
- Excluded by site principal investigator: Indicating that the site principal investigator excluded the subject prior to study completion because of medical complications or other reasons
- Excluded – Use of phototherapy: Indicating that the subject received phototherapy prior to the study visit.
- Other: Other outcome not listed.

Research staff will document on the **Site Enrollment Log** when the **Study Exit Case Report Form** had been completed on each subject by recording the date of completion in the appropriate box on the log for the corresponding study ID number.

B-2.6 Data management plan

The data coordinating center will be at the University of Washington. At each monitoring visit (except the site initiation visit and study closeout) photocopies of the following study forms will be made, and the photocopies provided to the data coordinating center by the study monitor: **Subject Enrollment Case Report Form, Study Visit Case Report Form**, and **Study Exit Case Report Form**. Photocopies will be made on all subjects with data recorded since the previous monitoring visit for each of these forms. The forms will be hand carried or sent by express mail service to the data coordinating center.

At the data coordinating center, data from the forms will be entered into Excel spreadsheets; there will be one spreadsheet for each form (i.e. 3 total). The coding keys for each spreadsheet are included in appendix 6.

Key variables for the study include the race and ethnicity of participants. Coding of race and ethnicity will be based on guidance provided by FDA.[27] Specifically, for parents who check "other" for race (as recorded on the **Subject Enrollment Case Report Form**) and provide a racial group for this response (e.g. "Haitian"), race data will be recoded based on the guidance provided by FDA and additional guidance as provided in appendix 6.

The following conventions will be used for coding race and ethnicity.

- Each major race group (American Indian/Alaska Native, Asian, African American/ Black, Pacific Islander/ Hawaiian Native, White, Other) will be coded as either "0" indicating not checked, or "1" indicating checked.
- If only "other" is checked and the only race specified is "Hispanic," "Latino" or other group that are designated as "Hispanic/Latino" ethnicity, all racial groups will be coded as 0 and the ethnicity will be coded as "1" indicative of Hispanic/Latino ethnicity.
- If at least one racial group is checked on the **Subject Enrollment Case Report Form**, and no box is checked for Hispanic/Latino ethnicity, ethnicity will be coded as "0", indicative of non-Hispanic/Latino ethnicity.
- If no race group is checked and no Hispanic/Latino ethnicity box is checked, all race and ethnicity groups will be coded as "9" indicating missing.

All data will be double entered onto separate excel spreadsheets; each spreadsheet will be printed and signed by the staff at the data coordinating center who entered the data. The spreadsheets will be imported into files on the Stata statistical software program (StataCorp LP, College Station, TX). The accuracy of data entry will be assessed by comparing double-entered databases in Stata (i.e. the value for each variable in entry 1 will be subtracted from the value in entry 2, results will equal 0). Any discrepancies will be resolved by reviewing the data as recorded on the photo copied CRF. If data on the photo copied study form are illegible or unclear, the research staff at the site will be contacted and the source document reviewed.

Once reconciled, data from the **Subject Enrollment Case Report Form** and **Study Visit Case Report Form** databases, will be merged. The age in hours of each subject when BiliCam data were obtained and when the blood was for TSB measurement was drawn will be calculated by subtracting the date and time of the respective event from the date and time of birth, and these ages in hours will be included in the data provided to the project biostatistician. To validate and clean the data, the age in hours for the BiliCam test and blood draw for TSB measurement will be checked for out range values (i.e. < 0 hours or > 192 hours); a similar process will be done to identify BCB values out of range (> 20 mg/dL). For identified cases, CRFs and source documents will be reviewed and the spreadsheet corrected using the **Data Clarification Form** as needed. Each spreadsheet will be "locked down" at the data coordinating center, printed out and signed. Spreadsheets including data from merged **Subject Enrollment Case Report Form** and **Study Visit Case Report Form** of subjects who have completed the study will be provided to the project biostatistician on a recurring basis (as described in section B-2.7). These spreadsheets will sent electronically from the data coordinating center, with de-identified data only, on study subjects; no PHI or other identifying information will be included. Prior to providing the spreadsheets, date and time of birth, date and time of collection of BiliCam images and BCB results, and date and time of blood draw for the TSB measurement will be deleted.

At the conclusion of the study, or as needed, the data coordinating center will send the spreadsheet containing data from the **Study Exit Case Report Forms** of study participants and the spreadsheet containing de-identified data from the merged **Subject Enrollment Case Report Forms** and the **Study Visit Case Report Forms** to the sponsor. The sponsor will lock down the spreadsheet; no changes will be allowed. Final copies of each of the spreadsheets will all the data included will be maintained at the data coordinating center.

Copies of completed **Adverse Event Case Report Form, BiliCam Incident Report Forms** and **Protocol Deviation and Other Problems Report Forms** will be checked by the study monitor to ensure they do not contain PHI, collated, and provided to the sponsor.

B-2.7 Analysis plan

For all enrolled subjects, a descriptive summary will be provided for gender, race, ethnicity, age (hours) at the time that blood was drawn for the TSB, age at the time BiliCam images were taken, and TSB and BCB values. The same summary will also be provided for all evaluable subjects, i.e. subjects with paired TSB and BCB values. Continuous measures will be summarized as mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized as frequency and percentage for each category.

The correlation coefficient (Pearson's r) and 95% CI will be calculated for paired TSB and BCB values for all evaluable subjects. This is the primary study outcome. Secondarily, the slope and the intercept (with 95% CIs) for the BCB vs. TSB regression line will also be calculated. Correlations between BCB and TSB among participants from different racial and ethnic groups will also be presented. A Bland-Altman analysis will be performed to characterize differences between paired TSB-BCB values; the mean bias and limits of agreement will be calculated.

When paired TSB and BCB data are available for 50 participants and again for 125 participants, interim analyses will be conducted for futility assessment only. There will be no interim superiority analysis and the study will not be terminated early due to favorable results. Therefore, no potential false positive error will be incurred. For each futility analysis, a locked down data spreadsheet will be provided by the data coordinating center to the project biostatistician for Pearson's correlation coefficient assessment. If the hypothesis used to power the study, i.e. an underlying true correlation coefficient of 0.90, is rejected at a 1-sided $p< 0.0025$ level, early study termination will be suggested to the sponsor for consideration. If a true 0.90 correlation is rejected at a 1-sided $p<0.00025$ level, early termination will be strongly recommended to the sponsor. The project biostatistician's communication to the sponsor will consist of one of the following three recommendations regarding the study conduct: (a) continue as planned, (b) early termination might be considered, (c) early termination is strongly recommended. When data collection has been completed at all study sites, the project biostatistician will receive a locked down data spreadsheet with all study data and will conduct the final analysis as described above. The project biostatistician will provide a report to the sponsor on the results of the analysis.

B-2.7.1. Acceptance criteria and sample size considerations

In studies supporting FDA 510(k) applications for the predicate device (JM-103), correlation coefficients ranged from 0.84 – 0.946.[1,2] Based on these studies, the acceptance criterion for demonstrating that BiliCam has comparable accuracy as the predicate device is: the lower limit of the 2-sided 95% CI around the point estimate for the correlation coefficient for the entire group of evaluable subjects will be $\geq$ 0.83.

It is planned to continue enrollment until 225 subjects (75 at each site) complete all study procedures (as defined in section B-2.1). It is possible that data on BCB and/or TSB measurements may not be available on a limited number of subjects who complete the study because of a laboratory issue with the TSB (e.g. specimen too hemolyzed for assay) or because of problem with the BCB value (e.g. out of range). The sample size of 225 enrolled subjects will ensure that paired BCB-TSB levels will be available on a minimum of 200 evaluable subjects for the primary analysis (correlation between paired BCB-TSB levels). Based on previous studies of BiliCam, it is estimated that the underlying true population correlation between BCB and TSB measurements is $\geq$ 0.90. With a sample size of 200 evaluable subjects, the chance for the lower limit of the 95% CI for the

observed correlation to be ≥ 0.83 is higher than 95%.

B- 2.8. Monitoring plan

All case report forms will be 100% monitored.

Each site will have 4 or 5 monitoring encounters

- Site initiation
- After 10-15 subjects have completed the study at a site
- After ~40 subjects have completed the study at a site (for sites with more than 40 complete subjects)
- After all subjects have completed the study at a site
- Study closeout

Note that site initiation and closeout visits may be remotely supported by the monitor. All case report form monitoring will be done on-site. Details of the monitoring plan are described in section E.

B-2.9 References

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C. RISK ANALYSIS

There will be blood draws exclusively for the study at sites using the Staged enrollment plan. There is minor pain from the blood draws. The blood drawing procedure may make some infants and their parents anxious. Both of these risks are transient. A study-specific blood draw is not necessary at the sites using the Simultaneous enrollment plan.

At all sites, there is the risk of loss of privacy from the collection of dates and time of birth, dates and time of blood collection for TSB levels that are ordered clinically, and race and ethnicity information collected for the study. There is also a risk loss of privacy of infants on whom image data are obtained and stored on the study computer server. However, the images will not include identifying information (i.e. the images do not include faces).

C-1.0 Minimizing risks

The risks of the blood draw for TSB levels at Staged enrollment plan sites will be minimized by having the blood obtained by phlebotomist with expertise in drawing blood from newborn infants. A maximum of 1 mL of blood will be obtained from the study participants. Blood samples will be identified only by a subject ID number to ensure privacy.

To minimize the risks from loss of privacy, all study files will be kept in a locked file cabinet in a locked office at each site. The key linking study ID numbers to a particular participant (i.e., the **Study Enrollment Log**) will be kept in a separate locked file cabinet and be kept at the site. This link (with medical record numbers to identify study subjects) will be kept at each site and not provided to the data coordinating center. Image data of study subjects contains only a small amount of skin of the subject's chest; no identifying information is included with the images. Images will be stored on a secure computer server. The data will only be accessible by the technical staff at BiliCam, LLC. Access will be by username and password only.

C-2.0 Description of study population

Overall, a maximum of 375 subjects will be enrolled in the study. A maximum of 150 subjects will be at any Staged enrollment plan site; enrollment will be discontinued at a Staged enrollment plan site when < 75 subjects have completed the study at that site. A maximum of 75 subjects will be enrolled at a Simultaneous enrollment plan site. Enrollment will be discontinued when 225 subjects have completed the study. All subjects will be < 192 hours old. It is anticipated that the number of male and female subjects will be approximately equal.

D. DESCRIPTION OF DEVICE

D-1.0 Summary description of the investigational device and its intended purpose

The BiliCam system is a smartphone application that employs the camera and LED to take images of a newborn's skin that can be used in automated analysis to estimate the bilirubin level in the newborn's blood. The system also comprises a rectangular paper color calibration card that is adhered to the newborn's sternum, with a rectangular hole in the middle, which frames the patch of skin that will be imaged and analyzed. The colors printed on the calibration card are used in the analysis as reference values against environmental variables.

The intended purpose of BiliCam is to be able to use an ordinary smartphone as a transcutaneous bilirubinometer, so that the result may be used by a medical practitioner in screening for neonatal jaundice that may require an intervention such as phototherapy.

D-2.0 Details concerning the manufacturer of the investigational device

The manufacturer of the device is BiliCam, LLC (dba Senosis), a limited liability company registered in the State of Washington whose primary offices are located at 601 N 34th St Seattle, WA 98103.

D-3.0 Name or number of the model/type, including software version and accessories, if any, to permit full identification

The mobile device will consist of an iPhone 5S model phone, with an operating system of iOS 10.3.2 and an iPhone 7 model phone with an iOS of 10.3.2 or later.

At the start of the study, BiliCam software app with version 3.0.0 will be preinstalled on the study devices. In the event that it is determined that modifications are necessary for the study to continue, all devices used in the study will be updated with the newer versions. Details of the change and impact will be described in an update to the Data Management Plan.

D-4.0 Description as to how traceability shall be achieved during and after the clinical investigation, for example by assignment of lot numbers, batch numbers, or serial numbers

The card used for each test will be affixed to the **Study Visit Case Report Form** for each subject after use. The version number of the software, as well as information for each specific phone that the sample was collected with will be recorded in the corresponding metadata file uploaded by the iPhone to the server.

D-5.0 Intended purpose of the investigational device in proposed clinical evaluation

BiliCam is a non-invasive transcutaneous bilirubinometer, which is intended as an index to predict serum bilirubin levels without regard to race, gender, or bodyweight.

D-6.0 Populations and indications for which the investigational device is intended

BiliCam is a non-invasive mobile application transcutaneous bilirubinometer which is indicated as an index to predict serum bilirubin levels in neonates > 35 weeks gestational age without regard to gender, race, or bodyweight. BiliCam provides a numerical measurement of predicted bilirubin level in mg/dL within a clinically relevant range that has been correlated with total serum bilirubin. The device is used by healthcare practitioners in the hospital, outpatient or home use environments. Neonates whose BiliCam test results are indicative of hyperbilirubinemia are evaluated by their physician(s) for appropriate patient management. The device is not indicated for use during or after exchange transfusions or phototherapy.

D-7.0 Description of the investigational device including any materials that will be in contact with tissues or body fluids

A small amount of adhesive on the paper calibration card will be in contact with the neonate's skin on the

sternum; some of the card itself may also rest lightly on the sternum. The adhesive is a hydrogel that has had biocompatibility testing and is currently used on other (non-investigational) high-volume production medical devices for neonates, such as electrodes. The adhesive is water soluble, so may be flushed with a small amount of water if necessary to help reduce adhesion and aid safe removal.

D-8.0 Summary of the necessary training and experience needed to use the investigational device

Instructions for use of the BiliCam app are shown in appendix 2 and will be reviewed by research staff at each study site. At the site initiation visit, the overall principal investigator will review use of the app on the study mobile phone with research staff, and research staff involved in obtaining BiliCam images will practice using the app, and demonstrate proficiency by obtaining BCB values on phantoms. The research staff at each site will also be taught on how to handle, apply and remove the calibration cards at the site initiation visit.

D-9.0 Description of the specific medical or surgical procedures involved in the use of the investigational device

No specific medical or surgical procedures are involved in the use of the device.

E. MONITORING PROCEDURES

A CRO will be selected by the Sponsor to oversee the conduct of the trial. An appropriate representative of the CRO (study monitor) will maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or retrieving data. An initiation (pre-study) visit will be made by the Sponsor (under the guidance of the study monitor) to discuss with the site investigator the protocol and the obligations of both the site. The site investigator will allow the study monitor to perform periodic, interim monitoring visits. The purposes of these visits are:

- To verify that written Informed Consent was obtained prior to each subject's participation in the trial.
- To assess the progress of the study.
- To review the compliance with the study protocol.
- To determine whether all adverse events were appropriately reported.
- To determine whether the Investigator is maintaining the essential documents.
- To discuss any emergent problem.
- To check the CRFs for legibility, accuracy and completeness.
- To validate the contents of the CRFs against source documents.
- To photocopy and collect completed CRFs.
- To assess the status of device accountability.

The site investigator will make available the source documents for inspection. This information will be considered as confidential. Violations of and deviations from the protocol must be notified to the study monitor as soon as possible.

The study monitor will perform a closeout visit at the time when all CRFs have been retrieved and all queries have been answered. All monitoring visits will be documented in monitoring reports.

E-1.0 Case Report Forms (CRFs)

CRFs will be provided for each subject. The study monitor will review the forms at each site visit. The appropriate CRFs will be completed for all subjects who sign informed consent, even if the subject fails to complete the study. No section of the CRFs will be left blank without an appropriate explanation by the site investigator, since the lack of such explanation may necessitate discarding an otherwise usable observation. If requested, copies of the CRFs will be made available to the appropriate regulatory agencies.

E-2.0 Auditing/inspecting

The site investigator will make all pertinent records available, including source documentation, for inspection by regulatory authorities and for auditing by the sponsor. This information will be considered as confidential. Audits/Inspections may occur any time from start to after conclusion of the study. When an Investigator signs the protocol, he/she agrees to allow regulatory authorities and sponsor auditors to inspect his/her study records.

E-3.0 Archiving of records

Copies of the protocol, subject identification codes, CRFs, source data, informed consent forms and other documents pertaining to the study conduct will be kept for the maximum period of time as required by the study center. This time period will be at least two years after the last approval of the marketing application of the investigational medical device and until there are no pending or contemplated marketing applications, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational medical device.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Originals of all documentation and copies of outgoing correspondence concerning the study will be stored and retained by the Sponsor in a safe area in the trial files for the lifetime of the product. In particular, the final report sent by the site investigator to the IRB/IEC will be retained by the sponsor, or the subsequent owner, for five years beyond the lifetime of the device.

F. MEDICAL DEVICE LABELING

Every mobile phone assigned to the study used at each study site as well as the envelope containing the calibration cards, will have a label applied indicating that the device is investigational and only for investigational use. A copy of the label is included in appendix 3.

G. IRB INFORMATION AND CONSENT MATERIALS

Information regarding the institution review boards that have reviewed the clinical validation study are shown in the table below. Approval notifications from each of the IRBs and copies of the current informed consent forms from each site are included in the sponsor's regulatory binder. Also included in the binder is the informational brochure that is provided to parents of eligible newborns at UWMC. As additional site(s) are added, the investigational plan will be amended to include the relevant IRB information.

IRB	Chairperson
Human Subjects Division University of Washington 4339 Brooklyn Ave NE Box 359470 Seattle, WA 98195-9470	Karen E. Moe, Director and Assistant Vice Provost for Research
Thomas Jefferson University Office of Human Research Institutional Review Board Jefferson Alumni Hall 1020 Locust Street, Suite M-34 Philadelphia, PA 19107	Walter Kraft, MD Director Office of Human Research

H. PARTICIPATING INSTITUTIONS AND SITE PRINCIPAL INVESTIGATORS

The name and location of institutions where study activities will occur are listed below. As additional site(s) are added, the investigational plan will be amended to include location information.

Thomas Jefferson University Hospital (site PI: Esther K. Chung, MD, MPH)
111 S 11th St
Philadelphia, PA 19107

University of Washington Medical Center (site PI: James W. Stout, MD, MPH)
1959 NE Pacific Ave
Seattle WA, 98195

University of Washington Medical Center-Roosevelt
Pediatric Care Center
4245 NE Roosevelt Way
Seattle, WA 98105

Data Coordinating Center--
University of Washington
Child Health Institute
6200 NE 74th Street
Seattle, WA 98115

I. FORMS AND OTHER DOCUMENTS RELATED TO DATA ENTRY

Other relevant documents are included in appendix 4. These documents are only applicable to the data coordinating center. The documents in appendix 4 include:

- Code keys for CRFs
- Guideline for coding race/ethnicity