Phase II Novel Low Cost QTc Meter for Long QT Syndrome Screening in Primary Care

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IRB Minimal Risk Protocol Template

General Study Information

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Study Title: Phase II Novel Low Cost QTc Meter for Long QT Syndrome Screening in Primary Care

Protocol version number and date: Version 4 7.24.2019

Research Question and Aims

Hypothesis: To specify, develop, and evaluate a diagnostic algorithm suitable for use in an inexpensive diagnostic instrument suitable for screening for LQTS in the primary care environment.

Aims, purpose, or objectives:

Blue Ox Health Corporation in collaboration with the Mayo Clinic, Minnesota Health Solutions, and the University of Rochester (New York), proposes to develop an inexpensive diagnostic instrument (the QTc Meter) specifically designed to support widespread screening for the QT interval in aiding of diagnosis of long QT syndrome (LQTS) in the primary care setting. Congenital LQTS satisfies several criteria that makes widespread screening worthwhile: LQTS is not rare (1 in 2,000 births), follow-on ECG diagnosis is feasible and ideally complemented by genetic testing, LQTS may cause up to 10% of sudden infant death syndrome (SIDS) and 15% of autopsy negative sudden unexplained death syndrome (SUDS) between ages 1 and 35, and highly effective treatments are available (1,2,3,4,5). Further, by stimulating cascade screening, diagnosis of affected infants may prompt identification of asymptomatic, but affected, and potentially at-risk family members.

The cost and complexity of existing diagnostic electrocardiography technologies make them incompatible with widespread screening for LQTS in the primary care setting. Existing FDA-approved single or multi-lead ECGs are not designed for fast, inexpensive, simplified QTc reporting. The proposed novel instrument will be purpose-built, with a validated QTc reporting automated ECG analysis program and simple low-cost display, for the specific task of QTc reporting in the primary care environment. We believe the proposed reusable battery powered handheld QTc Meter can be manufactured for under $50.

Infant screening using the proposed instrument will be cost-effective using conventional criteria, and with a QTc cutoff of 460 ms in two serial follow-on ECGs triggered by an abnormal value on the QTc meter, the number of false positives is estimated to be low (~1 in 1,000) (2). We envision the parents of newborn children being informed about LQTS, a treatable disease that can cause life-threatening arrhythmias in infants, children, and young adults occurring in 1 in 2,000 births, and informed that early diagnosis is achievable by adequate screening and any required follow-on diagnostics.

The objective of the proposed project is to further develop and evaluate a diagnostic algorithm suitable for use in an inexpensive diagnostic instrument suitable for screening for LQTS in the primary care environment. We plan to develop novel technology enabling the screening of newborns for the presence of abnormal QT/QTc interval prolongation. During this phase II study we propose to test a newly built prototype (upgraded from the

prototype used in phase I), validate the new algorithm in a cohort of 1,000 newborns/children and demonstrating the ability of the QTc meter to screen newborns for LQTS and help clinicians to improve patient management and save lives. The phase II project will finalize the algorithm design from phase I and fully validate its performance in a study informed by the phase I pilot evaluation.

Aim 1: Assemble a prototype system to enable the recording of the surface ECGs with the technical specification fitting the standard technical requirements for FDA-approved clinical ECG devices. Use the upgraded prototype developed base off results from the Phase I study to record ECGs in a cohort of 1,000 newborns/children to form a learning dataset for the Aim 2. This includes 500 control subjects and 500 with LQTS.

Aim 2: Evaluation of the usability and performances of the QTc Meter in a validation study conducted at the Mayo Clinic's LQTS Clinic

Objective:

We propose a novel inexpensive diagnostic device specifically designed to support widespread screening for LQTS in the primary care setting. The device will be physically small, easily cleanable, battery powered, and Bluetooth connected to obtain recordings on an associated device. It will connect to the patient with conductive pads that are held against the patient's chest (connections RA, LL, and RL). The objective of the proposed project is to specify, develop, and evaluate a diagnostic algorithm suitable for use in an inexpensive diagnostic instrument suitable for screening for LQTS in the primary care environment. The follow-on phase II project will finalize the algorithm design, test the newly developed prototype, and fully validate its performance in a study informed by the phase I pilot evaluation.

The envisioned end product will be based off of the results obtained from phase II of the study. At an infant well-child checkup in the primary care environment, a technician/study coordinator will press the device to the infant's chest for 30 seconds. The device will be paired with Bluetooth that can be connected to either an app or laptop that displays the results from that recording and stored via the cloud. It will be designed to be very easy to use. The proposed project concentrates on algorithm design. The phase I prototype will be assembled using an FDA approved ECG that the PI designed for QRS Diagnostic, LLC that will be modified to collect data in support the proposed development activities. A follow-up phase of the project will be used to test a more advanced prototype from the results obtained in phase I. Enrollment may also be discussed and arranged prior to the patient's visit via telephone.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*):

Infants, children, adolescents, and young adults are vulnerable to undiagnosed and potentially lethal cardiovascular diseases. The younger age range includes the clinically important group of infants at risk for sudden infant death syndrome (SIDS). Long QT syndrome (LQTS) is a genetic disorder characterized by QT prolongation, and is associated with potentially life-threatening cardiac arrhythmias that may lead to syncope, seizures, cardiac arrest, or sudden death. Although LQTS is potentially lethal, very effective therapies are available once LQTS is diagnosed. The development of an accurate and inexpensive instrument that screens for

LQTS, a treatable disease that occurs in 1 in 2,000 births, will enable earlier treatment for life-threatening arrhythmias in infants, children, and young adults.

The assembled research team at Blue Ox Health Corporation, MHS, the Mayo Clinic, and iCardiac Technologies Inc. (Rochester, NY) is well suited to achieve the proposed objectives. [redacted]

Infants and children are vulnerable to undiagnosed and potentially lethal cardiovascular diseases including the clinically important group of infants at risk for Sudden Infant Death Syndrome (SIDS). LQTS is a genetic disorder characterized by QT prolongation, T wave abnormalities on the ECG, potentially life-threatening cardiac arrhythmias (leading to syncope, cardiac arrest or sudden death) often triggered by emotional or physical stress, and the availability of very effective therapies (1). The onset of life-threatening arrhythmias is gene-specific and occurs mostly below age 15 (2). Mortality has been reduced from over 50% (for the highest risk subset) to approximately 1% over ~15 years follow-up for properly managed patients (1). On the basis of the identification of disease-causing mutations in infants with a QTc > 460 ms from a cohort of more than 44,000 infants with an ECG in the 3rd-4th week of life, the prevalence of LQTS has been estimated at about 1/2,000 live births in a population primarily of European descent (3). This allows a relatively simple calculation of how many new neonatal cases of LQTS can be expected each year in any country with a similar genetic background. It has been established, again by the presence of disease-causing mutations, that approximately 10% of SIDS may stem from LQTS-triggered sudden cardiac deaths (SCD)(4,5) and that LQTS contributes also to stillbirths (6,7). The combined observations that cardiac arrest or SCD is the sentinel event in 12-13% of affected patients outside the neonatal period (8), and that mortality is reduced dramatically among patients appropriately treated, suggest that early therapy has the potential to prevent SCD in the affected children (9). Thus, expectant management of a patient with a known diagnosis of LQTS without therapy is no longer acceptable (1). Recognizing this, treatment with β-blockers is now considered to be a Class I or IIa guidelines recommendation for almost all patients with a clinical diagnosis of LQTS (10). It goes without saying that affected individuals not yet diagnosed escape the possibility of being treated. Hence, an important clinical objective should be to identify the largest possible number of affected individuals at the earliest possible time.

The estimated prevalence of LQTS is approximately 1/2,000 live births (3). Disease-causing mutations were found in 43% of the infants with a QTc >470 ms, and 29% of those with a QTc between 461 and 470 ms; however, genetic screening was only performed in 14 of 28 (50%) infants in this latter QTc range. When this is added to the high probability that among the 196 non-genotyped infants with a QTc between 450 and 460 ms, there might be at least some LQTS mutation carriers, it is reasonable to assume that the prevalence of LQTS in

neonates may be higher than 1 in 2,000 (3). Finally, among patients with a definite clinical diagnosis of LQTS, approximately 20% are still genotype-negative. Thus, a LQTS prevalence of 1 in 2,000 in screened infants may still be a conservative estimate. With respectively 4 and 5.2 million live births per year in the United States and Europe (27 countries), the 1/2000 prevalence estimate predicts about 2,000 and 2,600 new cases of LQTS annually. Nationwide studies in Denmark and the Netherlands suggest that 50-60% of sudden unexpected deaths in children 1-18 years of age were due to inherited cardiac diseases (11).

Available data (3) suggest when to perform neonatal screening and how to design a reasonable protocol. In the 3rd-4th week of life, the QT pattern has stabilized which is still in the timeframe prior to the most common window for SIDS vulnerability (i.e. 2–4 months of age). As errors in measurement are possible and developmental changes may still occur (12), it is recommended to act only on the basis of a second ECG which should be performed whenever the first ECG shows a QTc of 450-460 ms. If the second ECG has a QTc (Bazett's correction) exceeding 460 ms (1.3/1,000, Figure 1), LQTS genetic testing involving at least the 3 major LQTS susceptibility genes is performed. If the QTc is >470 ms (0.7/1000), or if a mutation is identified, β-blocker therapy is recommended. In the more common situation that the first QTc is between 450 and 460 ms (0.4/1000), it may be decided to obtain one or more follow-up ECGs over a short period of time to make an evaluation contingent on the outcome of multiple ECGs. In all cases, family history is considered as well as ECG assessment in first-degree relatives. In the prior study, >40% of the infants with a QTc >470 ms had a disease causing mutation, and >90% of the infants whose QTc remained prolonged at 1 year of life had a positive genetic test (3). See Figure 1 below for a graphical representation of this protocol.

Even though screening in the neonatal period enables the identification of "at risk" infants prior to the peak incidence of SIDS (2-6 months), screening in the elementary schools has a strong rationale as well, especially when feasibility is concerned, as shown by the large program ongoing in Japan. The most recent report from the Kanazawa City Prefecture assessed the prevalence of genetically identifiable LQTS in a population of 7961 1st and 7th graders who underwent ECG screening and determined that at least 1 in 2653 subjects had an identifiable LQTS mutation (13). This is remarkably similar to the prevalence of LQTS found by Schwartz *et al*. in neonates (3), particularly considering that the data on SIDS (4) suggest that some LQTS neonates may not survive past 1 year of age. Approximately 12-15% of newly identified patients with LQTS have de novo mutations, while the rest are inherited paternally or maternally, which may be undiagnosed in other family members. Once the infant with LQTS is diagnosed, the family members can be screened phenotypically, and when a disease-causing mutation has been found in the proband, mutation-specific "cascade screening" (14,15) is performed in the family. The overall process has the potential to identify both neonates and older related individuals who are affected, and to importantly reassure those family members that test negative for the mutation, a multiple bonus that increases the benefits that accrue from this approach.

Significant questions have been raised regarding the effect of false positive findings as an unwanted cost of ECG screening for LQTS (16,17). It is important to understand that the threshold QTc used for diagnosis is the primary determinant of the test sensitivity and specificity. Raising the threshold QTc for screening diagnosis would increase the specificity and significantly reduce the number of false positives. The available data (3) point to a low expected false positive rate for those with a QTc >460 ms (<1/1,000, ~38/43,080 neonates in Figure 1), but to about 4.5/1000 for those with a QTc >450 ms. Thus, the false positive rate will be dependent on the QTc cut-off determined for follow-up.

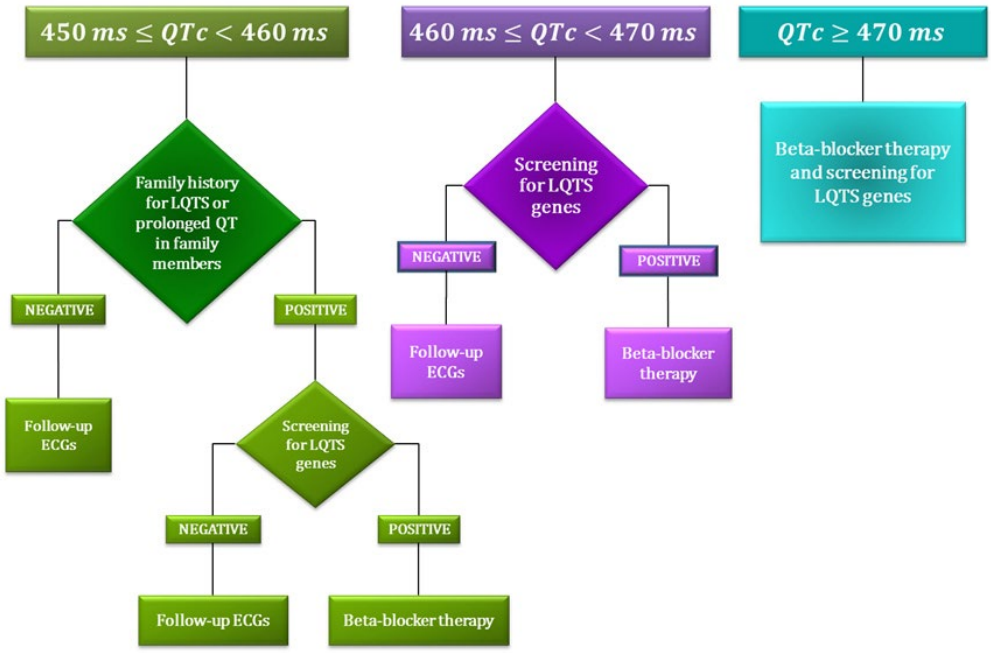


Figure 1: LQTS diagnostic protocol at 3 to 4 weeks of life.

Cost Effectiveness and the Commercial Potential of LQTS Screening

Cost-effectiveness analysis is useful to assess the societal cost of specific medical interventions. This is especially true when the performance of comprehensive, population-based studies may be biased by predetermined public opinion or government policy. Using parameters such as cost per life-year saved, or quality adjusted life-year saved, the value of the intervention can be assessed in relation to a standard threshold value that is societally accepted. For example, the cost of ECG screening in infants can be compared to the costs of vaccination for childhood infection, dialysis for chronic renal failure, or stenting for atherosclerotic coronary artery disease.

The available cost-effectiveness studies on screening approaches for the identification of asymptomatic youth at risk for SCD have had some common findings. First, because of its very low expense and relatively high sensitivity, the ECG is clearly a good candidate test to screen for the relevant diagnoses which may include other diseases besides LQTS. However, with the possible exception of Wolff-Parkinson-White syndrome, none of these diseases meet the criteria mentioned above for a successful screening effort as completely as LQTS. Second, the low prevalence of these diseases and imperfect specificity of the ECG necessarily result in some false positive screenings. As mentioned above, QTc values in excess of 470 and 460 ms have been associated with a low number of false positive findings, i.e. <1/1000 for two QTc measurements >460 ms (3).

Two earlier studies have examined directly the utility of ECG screening for LQTS in infants and newborns (18,19). Zupancic et al. estimated the cost of universal screening performed for LQTS at day three of life to be about $18,000 per life-year saved (18). This figure rose to over $50,000 per life-year saved if the efficacy of β-blocker therapy at preventing sudden death was reduced from 100% to 35%, illustrating the importance of

therapy efficacy. However, this study estimated the prevalence of LQTS at 1/10,000 (5 times lower than the current estimates), assumed that screening was performed in the maternity ward at day 3 of life, when the number of false positives is high (12), and targeted only decreases in mortality due to SIDS. Quaglini et al. provided a model with somewhat different goals and assumptions, based on ECG screening performed between 3 and 4 weeks of life and with the focus on prevention of sudden deaths due to LQTS not only in infancy (when they would be labeled as SIDS) but also later in life as well (19). They calculated a cost-effectiveness of under €12,000 per life-year (about US $16,000).

Neither of these informative models included the cost of genetic testing, which was not commercially available at the time. Using the paradigm in Figure 1, (9) and with the conservative estimate of 1.4/1,000 infants with a QTc >460 ms, one can expect approximately 6-7,000 infants per year undergoing genetic testing in the United States and in Europe. The advent of genetic testing will have differential effects on cost-effectiveness according to the country involved, as cost varies between €1,300 (US $1,700) in Europe and US $5,000 in the US. This will elevate the cost of the initial evaluation, but may possibly decrease total costs by appropriate reclassification of false positive patients, particularly as genetic identification of cases improves. Finally, it should be recognized that for all cost-effectiveness studies, the 1/2,000 prevalence of LQTS has direct and important effects on the results.

Commercial Potential

The proposed screening device is preliminarily planned be sold into primary care under the product line of National Biomedical Corporation. National Biomedical designed, manufactured, and sold the QRS Diagnostic (www.qrsdiagnostic.com) product line of cardiovascular diagnostic instruments (electrocardiographs, spirometers, ambulatory blood pressure meters, Holter monitors, etc.). National Biomedical has established worldwide distribution for the QRS Diagnostic electrocardiograph technology through a broad and diverse set of representatives and distributers. National Biomedical is seeking new cardiac-related products to engage its worldwide distribution. Other distribution plans are also under consideration.

(b) Innovation

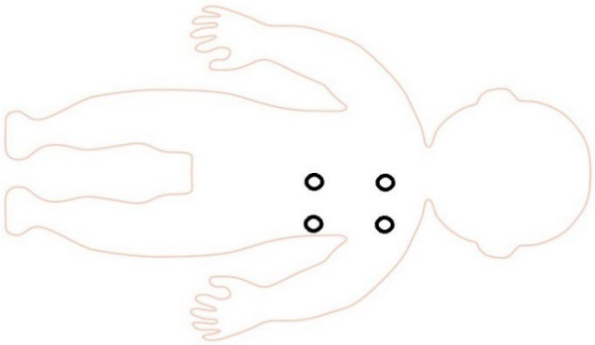
The proposed concept of conducting widespread LQTS screening using automated and focused analysis of just the patient's QTc in an inexpensive instrument specifically designed for the primary care environment is novel. To achieve QTc screening efficiently, it is desirable to create a specialized ECG acquisition and automated processing apparatus that is less expensive and easier to use in a primary care environment than existing diagnostic ECG machines. A simple instrument with press-to-chest electrodes (no lead wires) that provides a single output of QTc in milliseconds and a warning indicator does not exist presently. There are of course other single lead ECGs available, but they are not designed for simple, extremely low cost use in the primary care environment. No disposables are required in the proposed instrument. Recent technology innovations including a family of multichannel, simultaneous sampling, 24-bit, delta-sigma analogto- digital converters with built-in programmable gain amplifiers, internal reference, and an onboard oscillator, incorporate all of the features that are commonly required for ECG machines in a single very low cost integrated circuit (IC). With these high levels of integration, the new ICs enable the development of scalable ECG systems at significantly reduced size, power, and overall cost. The ICs suitable for the proposed application are about $4 each.

ECG diagnostics usually require a trained clinician to interpret the data in the context of the signs and symptoms of the patient. The tracings of the ECG provide information regarding heart rhythm, whether electrical impulses are conducting normally throughout the heart, or whether any part of the heart is contributing more or less than expected to the electrical activity. Modern ECG machines often include analysis software that interprets the acquired signals, but often manual over-reading of these conclusions is necessary. We will utilize the validated pediatric and adult Glasgow ECG interpretation algorithm in the proposed instrument, which has a demonstrated QTc reporting accuracy and is FDA-approved for diagnostic ECG applications. A primary care physician will screen patients using the proposed diagnostic instrument (the QTc Meter) at well child visits. The proposed specialized LQTS screening apparatus will cost less than $50 to manufacture and will utilize 3 patient leads to categorize diagnostic likelihood of LQTS via the diagnostic algorithm into low (less than a 1 in 2000 chance) or high (~50% chance) risk, as indicated by signal averaged, and time domain analyzed ECG determination of the QTc. A dedicated simple-to-use machine will be fast and reliable in the primary care environment. Such a machine does not exist presently.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

An updated prototype QT meter has been developed following the results obtained in phase I of the study. This new device, with its new enhancements, will be able to be paired with an associated app via Bluetooth and connected with a database in the cloud. Because this device is now Bluetooth enabled it will no longer need to be directly connected to the ECG machine. Phase II of the study will involve acquiring ECG data in a cohort of up to 1,000 newborns and infants (500 controls (non-LQTS) and 500 LQTS newborns and infants) that are being seen in the Gonda SL ECG Lab (or Baldwin Building)and enrolled during their appointment for a clinically indicated 12-lead ECG. A second arm of Phase II of this study will include approaching 50 healthy subjects at the Baldwin Building to seek interest in participation which will consist of (1) 30 second device recording to help further calibrate and test the device for optimal enhancement. These 50 subjects will not be required to have a clinical or research 12-lead ECG as we will be simply testing the efficiency and accuracy of the device. LQTS will be studied in order to assess the ability of the LQTS screener to accurately detect a patient with established QT prolongation in the context of distinct and varied T wave morphologies The advanced prototype will be placed in the same manner as the device used in Phase I of the study by being lightly placed on the child as pictured below. Similarly, we will use ultrasound gel to obtain a better reading, if applicable. Once completed, a photograph of the torso of the child will be taken from the same views as before (one aerial view and one side view) with neither the head nor the face in the picture. Coded ECG-tracings will be transmitted to the app and shared with Blue Ox Health Corporation and Minnesota Health Solutions as done previously in phase I. Additionally, coded tracings and data from the 12-lead ECG will be shared with Blue Ox Health Corporation and Minnesota Health Solutions to aid in comparison to device tracings and optimization of the algorithm. The 12-lead ECG will be obtained from the subject's medical record and coded before being shared with collaborators. Study coordinators will also review the patient's medical record to determine whether they have been diagnosed with a genetic disease.



Phase I Prototype

Phase II Prototype

Potential risks to the patient:

Potential risks of the protocol include skin reactions to the ECG electrodes or ultrasound gel
This device currently does not have an indicated use for patients with cardiac devices therefore to avoid this unknown risk we will not be enrolling any patients with a pacemaker/ICD.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

Screening will utilize the study coordinator and nurse of Mayo Clinic's LQTS Clinic who will review the schedule of returning, established LQTS children who would meet the study's eligibility criteria. If eligible, the infant/child's parents would be contacted at their annual clinical evaluation and informed of the study. If the parent agrees, consent will be obtained prior to the child's clinical 12-lead ECG in the Gonda SL ECG Lab. The study procedure, i.e. the application of the QTc Meter, will be initiated following consent.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 1,050 subjects

Subject population (children, adults, groups):
Newborns/Children ages 5 and under

Inclusion Criteria:

1. Infants/Children (Day 0-Age 5)
2. Long QT Syndrome (LQTS)
3. Newborns without LQTS (Controls)
4. Parental willingness to provide informed consent and follow the study protocol

Exclusion Criteria:

5. Children > 5 years old
6. Those with genetically elusive LQTS
7. Infants with congenital heart disease
8. Infants born <32 weeks EGA
9. Patients with a cardiac device implant (pacemaker/ICD)

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☐ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☒ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	X
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	X
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images	X	X
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

No statistical information

Over the course of the study, we will send de-identified recordings to Minnesota Health Solutions (MHS). We will work to finalize the algorithm design and fully validate its performance.

Power Statement:

Data Analysis Plan:

Endpoints
Primary:
Secondary: