ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☐ **Yes** ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreq@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) or MR from Masonic Institute for the Developing Brain (MIDB) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	

☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu*	**each have their own application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core? Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: bpic@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact:* fencl003@umn.edu	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	Capillary Refill Time Measurement Utilizing Mobile Application (Cap App) in Children
Principal Investigator/Faculty Advisor	Name: Jonathan R. Strutt, MD
	Department: Pediatrics
	Telephone Number: (314) 578-8045
	Email Address: strutt@umn.edu
Student Investigator	Name: N/A
	Current Academic Status (Student, Fellow, Resident):
	Department:
	Telephone Number:
	Institutional Email Address:
Scientific Assessment	I believe Scientific Assessment is not required.
IND/IDE # (if applicable)	IDE-NSR
IND/IDE Holder	N/A.
Investigational Drug Services # (if applicable)	N/A.
Version Number/Date:	Version 3, October 27, 2022

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	8/16/2022	data point collected for CapApp measurement & added research to the approved recruitment sign language	no
2	10/27/2022	Add CTSI monitoring	no

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ABBREVIATIONS/DEFINITIONS

- Cap App – Capillary Refill Time Mobile Application
- CRT – Capillary Refill Time
- ED – Emergency Department
- IV – Intravenous
- PPG - Photoplethysmography
- PI - Principal Investigator
- IND/IDE - Investigational New Drug/Investigational Device Exemption
- OIT - Office of Information Technology
- FDA - Food and Drug Administration
- IRB - Institutional Review Board
- AE - Adverse Event
- LAR - Legal Adult Representative
- DUA - Data Use Agreement
- NSR - Non Significant Risk

1.0 Objectives

1.1 Purpose: To determine the accuracy and precision of capillary refill time measurement using a mobile health application (Cap App) in a healthy pediatric population. This will be a cross-sectional study measuring the capillary refill time in a healthy pediatric population using both the Cap App and two additional manual methods which will serve as the comparison.

2.0 Background

1.1 Significance of Research Question/Purpose: A prolonged CRT is used to determine inadequate skin perfusion (1). It is a subjective physical exam finding which can be used to aid in the diagnosis of shock from any cause, such as hypovolemic (dehydration), septic, or hemorrhagic. This quick test which can be performed in any medical setting is vital to the assessment of circulation in children as recommended by the Pediatric Advanced Life Support course (2). Despite its clinical importance, there is low interobserver agreement among providers performing this routine clinical test (3). Additionally, Capillary refill time (CRT) is the time it takes for blood to return to tissue (on the fingertip, for instance) blanched by pressure. there is significant age and sex variation of normal CRT amongst otherwise healthy patients (1). The subjective nature of the CRT also limits the utility and improved clinical detail that might be obtained by quantifying the CRT more precisely. As currently employed, the clinician identifies the CRT as either normal or prolonged. This binary classification of CRT may be limiting its clinical usefulness. For instance, improved access to precise measurement of CRT may help improve the accuracy of the level of dehydration (mild/moderate/severe) and, thereby, reduce unnecessary emergency department (ED) visits and/or intravenous (IV) treatments. In addition, CRT has been utilized to assess, diagnose, or monitor many medical conditions in the pediatric population, such as hypovolemic, hemorrhagic, and septic shock.

The Cap App is a mobile smartphone application that we developed to measure CRT. It utilizes photoplethysmography (PPG) to calculate CRT. Previous research has shown that PPG — a technique that optically measures the blood volume changes in the microvascular bed of tissue via light absorption — can be achieved using the combination of a smartphone's flash and camera. To use such systems, a patient simply covers the flash and camera simultaneously using their finger. The amount of light that is reflected to the camera depends on the presence of two components: tissue, which remains constant over time; and blood, which varies over time. Therefore, the camera records and subsequently analyzes relative color changes to reproduce the PPG waveform, irrespective of a person's skin tone. This technique has been used to estimate heart rate (7), pulse-transit time (8), and even hemoglobin (9), and we have applied this approach in Cap App to measure capillary refill time.

Beyond making the capillary refill time assessment more precise, Cap App also makes the procedure more repeatable by ensuring that sufficient blanching has been achieved by using a combination of the PPG waveform and motion sensing. As the patient presses their finger against the camera, the phone vibrates, and its motion sensor measures how much the phone vibrates; harder pressure dampens the phone's vibration and causes a weaker signal (10). As blood leaves the fingertip, the amplitude of the PPG signal diminishes and eventually stabilizes to a brighter color due to blanching.

Improved access to precise measurement of capillary refill time will help expand the capabilities of experienced providers who are treating patients remotely through telehealth or less experienced providers treating patients in remote locations. This is especially important in low-resource settings or regions remote from specialty centers where providers may not be as experienced in the care of children. Triaging care for conditions such as pediatric dehydration is challenging due to lack of resources, especially in developing countries. However, even in well-developed nations, access to specialized care for pediatric patients is still lacking. Pediatric specialized care in the United States is largely regionalized. Most seriously ill children present first to community hospitals where resources and expertise to treat these children may be limited. In fact, more than 90 percent of emergency department visits for children in the United States are to non-specialty facilities (11). Admission rates for large specialty pediatric hospitals are 2-4 times larger than general emergency departments suggesting that the majority of providers caring for children have limited experience in treating higher acuity pediatric conditions (12). Additionally, in the setting of rising health care costs, many parents and other non-professional caregivers are increasingly seeking health information from non-traditional sources such as mobile smartphones.

2.1 Preliminary Data: A pilot study is ongoing on healthy adult volunteers. This study is not yet published in a peer-reviewed journal. The study's main objective is to compare CRT measured from Cap App versus manual visual assessment under differing temperature controls. The study has enrolled 19 participants, age 20-34; 9 female, 10 male. There is some variance in skin tone. We controlled for 5 temperature conditions (30°C, 27.5°C, 25°C, 22.5°C, 20°C) utilizing an ice bath to determine variance of CRT measurement under progressively colder temperatures. The results show that Cap App measures a longer CRT with greater variance in relation to the colder temperatures. It tends to overestimate CRT for darker skin tones. Overall, CRT is longer for Cap App than for a correlated, manual CRT measurement.

2.2 Existing Literature: Capillary refill has been utilized to assess, diagnose, or monitor many medical conditions in the pediatric population, such as hypovolemic and septic shock. Dehydration is one example of hypovolemic shock. The diagnosis of

pediatric dehydration is largely based on clinical findings. There have been multiple clinical dehydration scoring systems developed to assess for dehydration in pediatric patients, but none are particularly accurate at differentiating levels of severity (4). Capillary refill has been shown to be the best individual clinical predictor of acute dehydration in children (5). Previous research has shown that video recording of capillary refill time is a promising tool to diagnose dehydration in children. Video computation of capillary refill time has been shown to be more accurate at diagnosing significant dehydration in children than overall clinical assessment by trained pediatric specialists (6). Improved access to precise measurement of capillary refill time may help improve the accuracy of the level of dehydration (mild/moderate/severe) and, thereby, reduce unnecessary ED visits and IV treatments. Our aim with this study is to establish normative values of capillary refill as measured by the Cap App so that we may utilize its accuracy to improve the detection of peripheral perfusion abnormalities in conditions such as dehydration.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: Determining the accuracy and precision of a mobile health application (Cap App) to measure CRT in an otherwise healthy pediatric patient population.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): To establish normal values of CRT via Cap App for healthy children of varying age ranges, determine if subject characteristics such as skin tone, skin temperature, sex, or age affect the CRT measured via the Cap App, and determine if the CRT measured via the Cap App correlates to the manual measurement of CRT in healthy children at varying age ranges.

4.0 Study Intervention(s)/Investigational Agent(s)

1.2 **Description:** Cap App – mobile smartphone application used to measure CRT. The CapApp is a smartphone mobile application created through a partnership with the University of Washington, The University of Toronto, and The University of Minnesota. Management of the application will primarily be the responsibility of The University of Washington Ubiquitous Computing Lab led by Shwetak Patel, PhD and PhD candidate, Chunjong Park. Oversight of the project will be from The University of Toronto Assistant Professor of Computer Science, Alex Mariakakis, PhD. A standard Android smartphone running a custom smartphone application will be used for collecting fingertip videos, motion data, demographics (e.g., age, sex, temperature), and skin tone using the Fitzpatrick skin color scale. The app will start up and allow the user to enter a study ID and age, sex, race, skin tone, skin temperature, room temperature, core temperature, weight, vital signs (heart rate, blood pressure) and any underlying diagnosis. No other identifying information will be stored, including date of birth, name, audio, or fingerprint. The user is asked to place their right index finger on the

front camera. Once the app confirms that the finger is correctly placed, it asks the user to apply pressure against the phone. When the app detects whether the user is applying enough pressure for the specified time, it asks the user to relax the pressure. A function to notate any required assistance for the child in pressing on the smartphone to measure the capillary refill will also be noted. This will be needed especially for younger children and infants as it may cause a difference in how to interpret the results of the measurement. The app collects accelerometer/gyroscope data and video recording of the fingertip. The fingertip recording will not collect fingerprint identification information. The collected data will be uploaded to the cloud server on a secure data storage platform, Box.

The device, as used in this study protocol, does not meet the criteria of a serious risk device under 21 CRF 812.3(m) and therefore is a non-significant risk (NSR) device. The device meets the criteria of a NSR-IDE for the following reasons:

- This device is not intended as an implant and does not present a potential for serious risk to health, safety, or welfare of a subject.
- Is not purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject.
- Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety or welfare of a subject.
- Does not otherwise present a potential for serious risk to the health, safety or welfare of a subject.
- We will comply with the abbreviated requirements in 21 CFR 812.2(b).

1.3 Drug/Device Handling: The Cap App mobile software will be uploaded onto two smartphone devices. The smartphones will be locked with a passcode and only study team members will have access to that passcode.

Those devices will be stored in the Pediatric Emergency Department where only study personnel will have access to them for purposes of enrolling participants and collecting the study data.

As this device will be used at The Driven to Discover Research Facility at the Minnesota State Fair (2022), the device will be transferred and remain in possession of a study team meeting at all times.

4.1 Biosafety: NA

4.2 Stem Cells: NA

4.3 Fetal Tissue: NA

5.0 Procedures Involved

5.1 Study Design: The study design will be a cross-sectional study. The observation will be to collect the CRT from a population of healthy pediatric participants. Participants who meet the inclusion criteria will have their CRT measured using both the manual measurement (to include both human and computer annotation) and mobile health application (Cap App).

Study Procedures: **Cap App CRT measurement:** Children will be placed in a seated position, and their hand resting on a table top in a resting position. The research assistant will use a smartphone with the mobile health application (Cap App) to measure the CRT. The phone will be placed on a tabletop with the front facing camera face up. The subject's index fingertip will be placed onto the camera of the smartphone with minimal pressure. The finger will then be pressed firmly against the camera for a total of 5 seconds and then released from firm pressure while still contacting the camera with instructions from the Cap App. The research assistant then presses "stop" on the Cap App device. The Cap App will then measure the amount of time it takes for blood to refill the capillary bed as evidenced by the signal return to normal of light shining on the capillary bed. This measurement will be kept blinded to the researcher and be uploaded to a secure web-based cloud server, Box, for analysis. To establish the reproducibility of the index test (or the ability of the test to be accurately replicated), the CRT will be repeated at least twice on the index fingertip with at least 15 seconds between tests, and twice on the index finger of the opposite hand, all within 30 to 60 seconds of each other.

Manual CRT measurement: Children will be placed in a seated position with their hand raised slightly above the level of the heart on a table. A tripod will be set up for the smartphone to video record the capillary refill test by facing the table from the top. The recording will begin, and audio will not be recorded. The research assistant will compress the index finger of the participant for 5 seconds with transparent plastic and then release the pressure, after which the plastic will be removed from the field of view of the camera. The camera recording will then be stopped once the research assistant has determined the color has returned to its original color. To establish the reproducibility of the index test (or the ability of the test to be accurately replicated), the CRT will be repeated at least twice on 1 fingertip with at least 15 seconds between tests, and twice on the index finger of the opposite hand, all within 30 to 60 seconds of each other. The video, without audio, will be stored in the University of Minnesota's secure online storage platform, Box. For analysis the research study team will complete the following:

- Human annotation from manual CRT measurement: The video will be annotated blindly by a separate research team member than the one who performs the CRT manual measurement. The CRT will be measured as the

amount of time required for the index finger color to return to its pre-compressed color. The measurement will be annotated by a trained human from the video recording by measuring the CRT with a stopwatch, as is the current standard.

- Computer annotation from manual CRT measurement: The same video from the manual CRT measurement will be used for the computer annotation. A research team member will manually select a section of the finger for use in the analysis and then a computer will analyze the color using signal processing. This annotation will serve as the gold standard of what is possible for human visual CRT measurement.

Individually Identifiable Health Information: Electronic data collection forms will be used to collect all relevant variables to help interpret CRT measurements in the context of the healthy patient populations. In brief, the following is the information that will be collected:

1) For healthy participants:
   a. Demographics (race/ethnicity, gender, age).
   b. Temperature (environment, core, skin at finger).
   c. Clinical (weight, blood pressure, heart rate, oxygen saturation, skin tone)
   d. CRT measurement (manual video, Cap App)
   e. Any underlying diagnosis (medical history

5.2 Study Duration:

- Total study length: 15 months including 3 months for protocol development and IRB approval, 6 months for data collection, and 6 months for data analysis.
- Individual participant: time expected to complete the study is 30 minutes; 20 minutes for enrollment screening and consent and 10 minutes for the CRT measurements

5.3 Use of radiation*:* NA

5.4 Use of Center for Magnetic Resonance Research*:* NA

6.0 Data and Specimen Banking

6.1 Storage and Access: The individual participant study data will be collected in the smartphone application during the research encounter, under an assigned ID#. Once the data has been collected and uploaded to a secure web-based data storage site (Box) the individual devices will be cleared of any individual participant data.

1.4 Data: Study data will be uploaded from the smartphone application to a secure web-based platform (Box) for access by study team members only. The data (de-identified) will be shared with the University of Washington under a Data Use Agreement (DUA). The DUA is in process with SPA. De-identified data will be stored in Box for future use by other researchers. Data will be available immediately following study completion with no end date. Researchers, including those outside the study, whose proposed use of the data has been approved by the PI will have access to the data to achieve aims in the approved proposal. AHC-IE will not be used.

For publishing of data derived from the study: Publishing of these data may be required. Federal funders, granting agencies, and journal publishers increasingly require datasets be made publicly available-often immediately upon associated article publication. If this is the case, all data published will be fully de-identified.

6.2 Release/Sharing: Should the investigators pursue data sharing, future studies seeking to compile data acquired from this protocol will obtain IRB approval before doing so. In the event that this occurs, only investigators or study personnel listed in an IRB-approved protocol pertaining to the data compilation will have access to this data. The requested data will be released to the researchers in a de-identified manner. Any scientist who is willing to partner with a study investigator may submit a manuscript proposal or an ancillary study proposal. Once the PI approves the proposal, the investigator and the data coordinating center enter into a Data Use Agreement (DUA). After the signing of the agreement, this institution and coordinating team will distribute the requested data to the investigator. A nominal fee is charged for preparing the datasets.

7.0 Sharing of Results with Participants

7.1 There are no plans on sharing results of the individual participant study data or aggregate study data with the participants. The data will be kept blinded from the research team members at the time of collection and, thus, no information will be shared with the participants.

7.2 Sharing of genetic testing: NA

8.0 Study Population

8.1 Inclusion Criteria: Healthy children aged 1 month – 17 years.

8.2 Exclusion Criteria:

- Fever or hypothermia
- Chronic illness including cardiovascular or renal disease
- Severe injury or blood loss

- Dehydration (including vomiting and/or diarrhea)
- Raynaud's phenomenon
- Children who do not have a parent or legal guardian present to obtain consent

8.3 Screening: Convenience sample of participants presenting at the D2D: The Driven to Discover Research Facility at the Minnesota State Fair August 25 - September 5, 2022 will be screened for inclusion and exclusion criteria. All those who are eligible will have the opportunity to enroll. We will utilize a script to assist in the screening process to ensure that all information is presented accurately and uniformly to all potential participants.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.
Children	Primary focus of the research
Pregnant women/fetuses/neonates	Excluded
Prisoners	Excluded
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded
Non-English speakers	Excluded
Those unable to read (illiterate)	included but not the focus
Employees of the researcher	Excluded

Students of the researcher	Excluded
Undervalued or disenfranchised social group	included but not the focus
Active members of the military (service members), DoD personnel (including civilian employees)	Excluded
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	included but not the focus
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	included but not the focus
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	included but not the focus
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	included but not the focus

9.2 Additional Safeguards, if any, to ensure inclusion is appropriate:

Children: This research is designed specifically to assess the effectiveness of a mobile health application to measure CRT in children; therefore, children must be included in the study to answer the research question. Children are the targeted population for this study because the study aims could not be assessed without children. Study procedures have been minimized to exclude all unnecessary

procedures that would not contribute to the scientific objective. All participants will be provided assurance of confidentiality, the freedom to decline to participate and the right to withdraw at any time without penalty. Consent process for children is described in section 21.5

Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.: All efforts will be made to consent the patient or LAR during a non-stressful time. Extra caution will be taken as to not coerce the potential participant. They will be encouraged to ask questions of the research team or and discuss with their support if needed. Individuals who are noticeably nervous or stressed at that time will not be consented.

Those unable to read (Illiterate): Patients and/or their LAR who are illiterate may not be known, research staff will not be asking a direct question about literacy to potential participants. However, if it is made known to us that the patient or their LAR is illiterate, we will take extra care to go through the consent form and read it to the potential participant. An unbiased witness (non- study team member) will be present to attest that the consent form was described accurately. This witness will also sign the consent form.

Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare: Undervalued or disadvantaged people may not be known, research staff will not be asking a direct question about socioeconomic status to potential participants. The voluntary nature of study participation will be emphasized along with appropriate consent obtained as required per this protocol. Participation of not will not affect any relationship with this research team, the University of Minnesota or M Health.

Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior). Research staff will not be asking a direct questions of potential participants that could reveal such information. The voluntary nature of study participation will be emphasized along with appropriate consent obtained as required per this protocol. Participation of not will not affect any relationship with this research team, the University of Minnesota or M Health.

Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research. Research staff will not be asking a direct questions of potential participants that could reveal such information. The voluntary nature of study participation will be emphasized along with appropriate consent obtained as required per this protocol. Participation of not will not affect any relationship with this research team, the University of Minnesota or M Health.

Individual or group with a serious health condition for which there are no satisfactory standard treatments may be included unless exclusionary (see section 8.2). The study is non-interventional and will not impact care or treatment of the child, therefore felt that can be included in study enrollment. If there are questions, the research team will defer to the investigator for inclusion.

9.3 If research includes potential for direct benefit to participants, provide rationale for any exclusions indicated in the table above: NA/no direct benefit to participation

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: A minimum of 240 participants are needed for data analysis and we anticipate needing to consent 300+ participants to meet that goal to account for errors in data collection, data upload, and/or participant withdrawal. We will attempt to match participants by age group and skin tone to control for expected variance of CRT measurement.

11.0 Local Recruitment Methods

11.1 Recruitment Process: Convenience sample of participants presenting at D2D: The Driven to Discover Research Facility at the Minnesota State Fair, August 25 - September 5, 2022.

11.2 Identification of Potential Participants: All participants interested in enrolling in our study presenting at the D2D: The Driven to Discover Research Facility at the Minnesota State Fair will be screened using the inclusion/exclusion criteria. We will then approach the parent/guardian for consent of children meeting the inclusion criteria.

11.3 Recruitment Materials: A conspicuous study sign will be made. The sign will have the following verbiage: “Cap App: a mobile health smartphone application to measure finger blood flow in children. You may be asked to participate in an optional research study to learn more about the utility of a new smartphone application that could one day improve the diagnosis of several medical conditions in children, including dehydration. ” This sign will be in the clearly visible in the D2D Research Facility at the Minnesota State Fair

11.4 Payment: No payment will be provided but all participants will receive a complimentary University of Minnesota Backpack provided through D2D.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

● If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant. This may include if there are any signs of discomfort (i.e. crying, tantrums, fits, screaming).

● If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

12.2 Withdrawal Procedures: If a participant/parent/guardian wishes to withdraw or we determine that the participant should withdraw, we will terminate data collection and discuss with the participant the reasons for withdrawal. All data collected up to that point will be used in analysis. This will be made known in the consent form.

12.3 Termination Procedures:

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the funding agency. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. The study team will notify the participants of the study termination.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and/or data quality procedures are addressed and satisfy the sponsor, IRB and/or FDA.

Data collected for the study prior to the study termination will be handled in the following manner:

- If the study is terminated due to safety reasons, the data related to AEs will be evaluated.

If the study is terminated for any other reason, the regulatory and/or institutional document/data retention policies will apply.

13.0 Risks to Participants

13.1 Foreseeable Risks:

Although we cannot eliminate the loss of confidentiality or privacy, this study does involve the collection of private health information. All personal information will be assigned a random study identification number and stored on a secure database. The personal information of the participants will not be recorded in the study database.

The smartphone camera will only record participants' hand/fingertip so no sensitive information should be recorded by the smartphone camera. The smartphone has ability for video only so that audio is not applicable. Nevertheless, participants will be made aware of the nature of the video recordings ahead of time and will have the option of having video recordings re-done or deleted.

We will provide a brief explanation of the procedure to the participants old enough to understand (age >3 years) so that they can know what to expect with finger compression. The explanation will include language similar to: "Your fingertip will be squished tightly for 5 seconds, but then it will stop. You'll have this done four times on both your right and left finger, but we may ask you to have it happen again."

13.2 Reproduction Risks: NA

13.3 Risks to Others: NA

14.0 Potential Benefits to Participants

14.1 Potential Benefits: There are no direct benefits for participation in this study. This information will be used to help determine effectiveness of a mobile health application at measuring CRT in children.

15.0 Statistical Considerations

15.1 Data Analysis Plan: We plan to utilize a Biostatistical Design and Analysis Center biostatistician from the Clinical and Translational Science Institute in the statistical analysis of our data. We will compare the manual method of CRT (human annotation with a stopwatch and computer analysis) and Cap App measurement of CRT amongst each individual subject. We will then create a normal range of Cap App CRT based on

age of the subject in one of five categories (1-3 months, 3-12 months, 1-5 years, 5-12 years, and 12-17 years), sex (male or female), and race (skin tone). We will include a description of the primary diagnosis, vital signs (heart rate, blood pressure, oxygen saturation), temperature (room, patient core, and skin), and second, third, and fourth measurements of CRT (used for intra-rater reliability). Missing data will be documented as noted and the record will be excluded from analysis as applicable. Minimal missing data is expected, so missing data will not be imputed.

15.2 Power Analysis: The goal of this study is to determine the precision of the capillary refill time measured via the smartphone application, so no formal power calculation was performed.

15.3 Statistical Analysis: We will recruit pediatrics patients aged 1 month to 17 years who are presenting to the D2D: The Driven to Discover Research Facility at the Minnesota State Fair. Descriptive statistics will be used to summarize the data collected. For the primary outcome, we will calculate mean CRT along with 95% confidence intervals, both overall and by age group, sex, and skin tone. We will attempt to enroll a minimum of 48 patients per age group for a total of 240 patients. Initial results showed an average standard deviation of 0.663 seconds across all patients at normal hand temperature. When the sample size is 48, a two-sided 95% confidence interval for a mean will extend ± 0.188 seconds. For a total sample size of 240, a two-sided 95% confidence interval for a mean will extend ± 0.084 seconds. Human annotation of a video recording using a stopwatch will be used to measure the manual CRT measurement and we will perform computer annotation of the video recording as a gold standard. For human and computer annotations we will calculate inter-rater reliability by repeating annotations with a different observer on 10% of a random group of CRT measurements. Inter-rater reliability will be evaluated using intraclass correlation coefficients (ICCs) and Bland–Altman plots.

15.4 Data Integrity: The research assistant will obtain study eConsent and fill the data collection forms which will be embedded into the Cap App and will be password protected. The data forms, video recordings for human and computer annotation, and Cap App CRT measurement will then be uploaded to a secure web-based data storage platform, Box. The research assistant will erase the data on the smartphones every shift and will store them in the in a secure location at all times. The *consent forms, assent forms, and case report forms* will be electronic (UMN REDCap eConsent). No paper copies will be utilized.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

X I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

X I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe: Describe in detail the source of the information.

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

Only participants who voluntarily approach our study team members with interest in participating in our study will be screened.

16.4 Approximate number of records required for review:

We anticipate screening approximately 300 children for enrollment with a total enrollment goal of at least 240 participants, with aim for 48 in each of five age categories (1-3 months, 3–12 months, 1 - 5 years, 5-12 years, and 12-17). No access to the child's medical record will be required as enrolled during the D2D State Fair location.

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

X Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants. Participants will express interest in person by presenting to the D2D: The Driven to Discover Research Facility at the Minnesota State Fair.

16.6 Explain how the research team has legitimate access to patients/potential participants: The research team will be permitted to access sources of private information because all participants will be required to sign a HIPAA waiver at the time of informed consent.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

X In the University's Box Secure Storage (box.umn.edu)

X Store **X** Analyze **X** Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

X Other: see mobile device below

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

X I will use a mobile device such as a smartphone not previously listed: The demographics, vital signs, underlying diagnosis, and CRT data (including video for the manual CRT measurement) will be collected from a smartphone which is running the Cap App mobile phone application. The data collected will be de-identified and uploaded to a secure Box platform hosted by UMN.

16.8 Consultants. Vendors. Third Parties. : A DUA will be signed to share de-identified research data with The University of Washington and The University of Toronto, who are collaborators on the CapApp.

16.9 Links to identifiable data:

All data will be de-identified. Study staff will assign an identification code for each participant to identify each individual record but it will not be used to link back to each individual participant. That same identification code will be transferred into the Box database. Any internal data reports will use only these codes and will not use any identifiable information. Any external data reports, abstracts, publications, presentations, etc. will present de-identified, grouped, and/or aggregate data. Any reports to the University of Minnesota IRB (such as Adverse Event reporting and annual renewal reports) will be kept confidential; they will not include participant- identifiable information; only the participant's identification code will be used

16.10 Sharing of Data with Research Team Members Only IRB-approved members of the study team will have access to the data through the methods already indicated in this section.

16.11 Storage of Documents: Electronic documents will be stored in a secure database only accessible to research staff. We will maintain the de-identified patient characteristic data, de-identified video, and Cap App data for future use by other researchers (in UMN Box).

16.12 Disposal of Documents: We will erase individual data forms from electronic smartphones upon transfer to Box file.

17.0 Confidentiality

17.1 Data Security:

Computers used will be University owned and meet University compliance requirements and pertinent external regulations. All computers are password protected and meet a basic level of security to protect the integrity of the data and network. These precautions also procure a high level of security to protect the integrity of the data and network as well as comply with OIT and data storage requirements within Fairview and the University of MN. Data will be stored on a password protected computer behind a firewall protected user drive.

Training: All study staff will be appropriately trained to this protocol and its requirements, including maintenance of participant confidentiality.

Authorization of access: Only designated IRB-approved staff will have access to the data. The data collected will not be reported to any medical provide nor provided to the patient or adult/legal guardian. The CRT measurements collected will be kept blinded to the participants and to the research staff and will not be interpreted or cause any change to the treatment or care of the child.

Password protection/encryption/physical controls: All data will be stored in the UMN Box system which is secured and HIPAA compliant. Consents will be retained in the HIPAA compliant REDCap platform that will only be accessed by the study team.

Confidentiality:

Individual participant information obtained because of this study is considered confidential. Information will be accessible to authorized parties or personnel only. All records will be identified in a manner designed to maintain participant confidentiality.

No paper records will be kept.

Separation of Identifiers and data:

Participants will be assigned a unique identifier. Any participant records or datasets will contain the identifier only; participant names and associated unique identifier will be kept on a separate log (Box). The capillary refill measurements will be kept blinded to the research team member and no action will be taken on aberrant measurements.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring.

Data collection is the responsibility of the study staff under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. This includes ensuring that the study activities are occurring as per protocol.

The study team will also utilize the University of Minnesota CTSI monitoring services for external monitoring. The monitors are trained in GCP and federal regulatory requirements through the University of Minnesota Clinical and Translational Science Institute (CTSI), and is supported by the NIH Clinical and Translational Science Award at the University of Minnesota: UL1TR000114.

Monitoring will provide review of the study protocol and participant enrollment and data collection. This use is in order to ensure that the study team is conducting the study according to protocol, SOPS and federal and GCP regulatory requirements.

Monitoring will be conducted at minimum on a 6 month basis with request by the investigator or monitor to increase monitoring if there are concerns. They will be provided access to all study files, regulatory and participant, and conduct their visits in-person or remotely based with the study team available for questions and instructions. The PI will communicate with the monitors to discuss any findings. The monitors will allow a process of addressing any findings at the time of the visit and then provide a final follow-up report to the study team. The study team will address prior to the next visit. This report will be provided to the University of Minnesota HRPP quality assurance program as per institutional requirements.

18.2 Data Safety Monitoring.

Based on the minimal risk nature of this study, data safety monitoring will be under the supervision of the principal investigator. The investigator will review data with the study team and if any noted adverse events do occur, the study may be suspended and/or terminated (section 12.3) with appropriate reporting to the IRB and any study participants.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: Confidentiality of the research participants will be maintained. All data will be stored electronically on a secure data storage platform and will

not be released without consent of participants. Data to be used in scientific presentations or publications will not contain participant identifiers. All material will be used exclusively for research. Data obtained will be stored in a confidential database without direct identifiers. The principal investigator and designated study staff will have access to the linkages, which will be stored in a separate, secured location. Hard copies of data will not be kept. Any study files that will be shared with the University of Minnesota will remove patient identifying information.

19.2 Access to Participants*:* All research staff listed on this application are trained in research ethics and are eligible to conduct human subject research. Participants will be fully informed of the ways in which their data will/may be used during the informed consent process. The research team has been trained in conducting these conversations and the participants are also assessed for their understanding of consent prior to initiating any study procedures.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: If research-related activities result in an injury, treatment will be provided to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.

20.2 Contract Language: NA.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

Participants will self-report with interest at the D2D: The Driven to Discover Research Facility at the Minnesota State Fair.

- The consent will take place in the research space provided at the D2D: The Driven to Discover Research Facility.
- There is no built-in waiting period available between informing the prospective participants and obtaining the consent. If the subject requests a waiting period to help make an informed decision, a reasonable time will be allotted to accommodate that request as deemed appropriate by the treating provider.
- We will provide a copy of the current ICF to the participant, in advance if possible.
- ICF will be read to the participant after which questions will be invited and responded to.
- The participant will be given time to discuss consent with others, including taking ICF home to consider.
- The researcher will determine if the potential participant understands the information presented through the consent process and

comprehends study details. It is under the discretion of the researcher, and per D2D requirements, that if there is suspect of alcohol intoxication, consent will not proceed at that time.

- We will obtain consent from one parent/legally authorized representative and assent from the participant if old enough.
- This will be obtained by electronically in-person utilizing the D2D provided devices (i.e. iPads) with electronic signature capture.
- An electronic copy of the signed ICF/HIPAA forms will be emailed to the participant.
- We will ensure ongoing consent though voluntary participation in the study including performing the procedure. We will ensure voluntary participation at each stage of the study through verbal confirmation.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): NA

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): A script will be used to screen potential participants for enrollment, prior to obtaining consent. This script will ensure that all information is presented accurately and uniformly to all potential participants. No PHI or study procedures will occur until formal consent process is conducted and signed consent/assent is provided.

21.4 Non-English Speaking Participants: Non-English Speaking will be excluded at the time of D2D State Fair based on inability to ensure appropriate interpreter services for consent and participation. When services or location allows for the potential enrollment of non-English speakers, the study team will complete a modification for enrollment.

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

Infant to 7 years old

Parent(s) interested in hearing more about the study will be informed in detail of the purposes, procedures, and potential risks of the study and of their rights as parent(s) of a research participant. This will take place in a private and confidential room. Parents will have the opportunity to carefully review the parental permission form, ask questions, discuss the study with others or think about it prior to signing. The study team will ask the parent(s) questions about the parental permission form to assess comprehension. If the study team feels the parent(s) understands what's being asked of their child, one or both parent(s) and study team will sign the parental permission form. Parents will be given a signed copy of the parental permission form. Parent(s) will also be instructed that they are free to withdraw their permission and discontinue their child's participation in the study at any time.

Child's assent will not be obtained. Child's dissent will be honored if parental guardian and/or study team member agree that undue harm or distress will be placed on the child exhibited through behavior such as crying, tantrum, fit, or screaming.

8-17 years old

Parent(s) and children interested in hearing more about the study will be informed in detail of the purposes, procedures, and potential risks of the study and of their rights as parent(s) of a research participant. This will take place in a private and confidential room. They will have the opportunity to carefully review the parental permission and assent form, ask questions, discuss the study with others or think about it prior to signing. The study team will ask questions to assess comprehension. If the study team feels the parent(s) understands what's being asked of their child, one or both parent(s) and study team will sign the parental permission form. Parents will be given a copy of the signed parental permission form. Parent(s) will also be instructed that they are free to withdraw their permission and discontinue their child's participation in the study at any time.

The assent from the child or adolescent will be obtained when this is appropriate and when the potential participant is capable of providing assent. The determination of appropriateness and capacity of children in the study to provide assent is made by the research study member taking into account the ages, maturity, and psychological state of the children involved. Child's dissent will be honored.

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: NA

21.7 Adults Unable to Consent: NA

22.0 Setting

22.1 Research Sites: D2D: The Driven to Discover Research Facility at the Minnesota State Fair, August 25-September 5, 2022.

22.2 International Research: NA

23.0 Multi-Site Research: NA

24.0 Coordinating Center Research: NA

25.0 Resources Available

25.1 Resources Available:

The D2D Research Facility at the Minnesota State Fair provides a turn-key research space for conduct of minimal risk human subjects research that is appropriate for a state fair environment.

Services include:

- Free admission to the State Fair for staff (up to 4 tickets per shift);
- Furnishings, basic anthropometric equipment, and supplies;
- iPads linked to consent forms and survey instruments;
- U of M secure high-speed wireless and hardwired internet access;
- Refrigerator and freezer space for on-site sample storage;
- Guidance in obtaining IRB approval;
- Consultation on maximizing your recruitment goals, your IRB application, designing your research area, working in the state fair setting, and more;
- Compliance with state fair rules and regulations.

All persons assisting with the research will be adequately informed about the protocol, the research procedures, and their duties and functions. This information will be shared with the researchers prior to the start of the study and the primary investigator will be available for any questions relating to the study protocol or procedures at any time throughout the study period.

26.0 References

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