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CALIPER Mother & Child Health Initiative:

Closing the Gap in Maternal Reference Standards of Health and Disease

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EXECUTIVE SUMMARY

Clinical Problem: Clinicians, including obstetrician-gynecologists and family physicians, depend on accurate reference standards (i.e. normative ranges or intervals) to interpret laboratory test results in pregnant women and make appropriate clinical decisions for both mother and child. Unfortunately, evidence-based reference intervals are lacking in pregnant populations. This should be regarded as a major clinical problem, compromising the quality of health care for pregnant women and their newborns.

Central Hypothesis: Maternal reference values from healthy pregnant women for the majority of routine laboratory tests are significantly different from those of general adult populations, compromising maternal/fetal care and necessitating the establishment of accurate reference intervals in these periods.

Overall Objectives:

1) Establish a robust database of trimester-specific and postpartum maternal reference intervals for laboratory markers typically measured to assess health during pregnancy.
2) Disseminate reference interval data to hospitals and clinical laboratories across Canada, USA, and globally using novel knowledge translation strategies including web and mobile applications (www.caliperdatabase.org).

Study Impact: This study will result in a rich database of healthy normative values in pregnancy. This will beneficially impact clinical practice through improved laboratory test interpretation, leading to more appropriate follow up/treatment.

RATIONALE/RELEVANT BACKGROUND

At the Hospital for Sick Children, we recognize that a healthy start to a baby's life begins with a healthy pregnancy. Despite efforts to improve the standard of maternal healthcare, maternal morbidity and mortality remain significant healthcare concerns in North America. Studies have shown that delayed, missed or erroneous diagnosis of pregnancy complications can contribute to preventable morbidity. Improved clinical decision-making can aid in minimizing preventable pregnancy complications, leading to improved health of both the mother and child.

The standard of maternal healthcare worldwide relies heavily on laboratory testing and accurate test result interpretation. Throughout pregnancy, several tests are used for the diagnosis and monitoring of pregnancy-related complications (e.g. biochemical markers, electrolytes, coagulation factors, hematology parameters and markers of infection, eclampsia, thyroid and liver disease). Early recognition of disease in pregnant women is important not only for maternal health, but also fetal development. To ensure optimal diagnosis and monitoring of pregnant women, laboratory test results should be interpreted based on accurate and robust health-associated benchmarks known as reference intervals (i.e. normative values or reference standards). Reference intervals, commonly defined as the central 95% of test results in a healthy reference population, must reflect physiological changes in biomarker concentrations and often require stratification by important covariates, such as age and sex. Unfortunately, there is a paucity of evidence-based reference intervals for many biomarkers of health and disease in pregnancy, creating the potential for erroneous result interpretation and preventable complications. Currently, maternal reference standards used by hospitals and clinics globally may be: a) derived using inappropriate populations (adult males, non-pregnant women, or hospitalized patients), b) non-existent for several emerging biomarkers of health and disease, and/or c) determined using small sample sizes or less accurate and/or out of date methodologies.

Studies have shown that the use of inappropriate reference intervals can lead to erroneous diagnosis and harmful medical decisions. Pregnancy is known to be associated with significant changes in biochemical and hematological measures of health. As a result, associated reference intervals must accurately reflect this dynamic physiology at each trimester to avoid clinical misinterpretation. For example, interpretation of maternal thyroid stimulating hormone (TSH) results based on non-pregnant reference intervals can result in missed diagnosis of hypothyroidism and lead to adverse outcomes for mother and child (e.g. pregnancy loss, preterm birth, severe fetal neurocognitive impairment). While a few studies have established reference intervals for endocrine and hematological parameters in pregnant women, results are often conflicting and do not follow appropriate statistical methodology recommended by the Clinical and Laboratory Standards Institute (CLSI). Additionally, data is lacking for many key biochemical parameters leading to huge knowledge gaps. As a result, reference intervals in use by clinical laboratories continue to be based on very small sample sizes, older analytical methods that are no longer relevant, and/or single ethnicities. Taken together, these critical gaps fundamentally compromise the ability of clinicians to make accurate medical decisions during pregnancy and early life, thereby contributing to increased patient risk, mortality, and healthcare costs.

The Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER, REB# 1000010867) was founded at the Toronto Hospital for Sick Children in collaboration with a number of other pediatric centers in 2009 to address critical gaps in reference intervals for pediatric laboratory test interpretation. CALIPER has since recruited and sampled over 12,000 healthy children and adolescents and established pediatric reference intervals for over 185 laboratory tests on several analytical platforms, gaining international

recognition. The rigorous process undertaken to partition reference intervals by age and sex has resulted in a dataset of unprecedented richness, underscoring the importance of growth and development on circulating biomarkers of pediatric health and disease. Knowledge translation through over 50 publications in high impact journals and innovative tools including the CALIPER online database (www.caliperdatabase.org) has led hospitals around the world to adopt CALIPER data in routine clinical practice. In the current study proposal, the research team behind CALIPER will apply a very similar outreach and methodological approach to establish robust reference standards for pregnant women in the Greater Toronto Area and Hamilton/Niagara regions. The evaluation of reference values for important laboratory tests in pregnancy will greatly contribute to the accuracy of test interpretation as they can be immediately implemented following validation, directly impacting healthcare.

STUDY DESIGN & METHODOLOGY

Phase I: *Participant Recruitment & Sample Acquisition*

Recruitment – In Person

As the goal is to obtain samples from healthy pregnant women, the recruitment of study participants will take place in the wider community, including:

I. Doctors' offices and OBGYN clinics at healthcare centers in the Greater Toronto Area and Hamilton/Niagara regions
II. Midwifery centers in the Greater Toronto Are & Hamilton/Niagara regions
III. Prenatal care centers & parenting clinics in the Greater Toronto Are & Hamilton/Niagara regions
IV. On social media through CALIPER accounts via Twitter, Facebook, and Instagram

Only the SickKids CALIPER program will be involved in sample collection using our CALIPER phlebotomists at different collection sites, as listed above. Various groups, including midwife centers, OBGYN clinics, and other prenatal centers/groups, will be contacted only for purposes of promotion and recruitment. We are not formally collaborating with these centres, and there will be no exchange of funds, materials, or data. We will be simply promoting the study to these groups to recruit participants. Expecting mothers will be contacted through such centres but will be consented individually to participate in the project by the SickKids study team. This is the approach we have successfully used for the REB approved CALIPER study (REB #1000010867) to recruit children and adolescents from the community over the past 10 years. Similar to CALIPER, a Note-to-File will be submitted to REB each time the study team holds an off-site event. The Study Site Log will also be submitted to REB with the annual renewal application. Additionally, all clinic sites (doctor's offices, prenatal centers, midwife clinics etc.) will be documented in the Study Site Log, according to year of collection. The log will contain location information for each clinic site, as well as the number of participants recruited at each site (note: number of participants recruited at each site will be documented immediately following each clinic). All prospective clinic sites will be contacted by email and/or phone to discuss the project. In-person meetings with the prospective centers will also be arranged. Following discussion, approved promotional materials, including brochures and flyers (see documents attached), will be circulated to clinic sites.

Promotional materials will also be circulated using CALIPER social media accounts after approval from the SickKids Social Affairs Office. Individuals who are interested in participating can call or email the contact information on the brochure/flyer and schedule a time to visit the study team at SickKids for on-site

collection. We will ensure that all posts containing information other than the provided recruitment poster/flyer will be submitted to REB for approval prior to posting.

Recruitment – Virtual

To improve recruitment numbers and reduce in-person activity, a collaboration with LifeLabs has been executed wherein participants can consent and complete study materials remotely. The process will occur as follows:

1. Interested participants from REB-approved promotional materials circulated to centres as per above will send an email to motherand.child@sickkids.ca through our website or directly
2. The research team will send potential participants the consent form electronically through email via a link to an external RedCap.
3. The research team will schedule a time to complete the virtual consent process through telephone or videoconference.
4. At the appointment, the research team will confirm the identity of the participant and review and discuss the consent form in detail
5. After all questions are answered and the research team feels confident the participant understands the study, each person will sign and date the external RedCap form (including research member upon return with a note indicating consent was obtained virtually)
6. Following consent, the participant will be forwarded two external REDCap questionnaires (see REB-approved Contact Information Form and Health Questionnaire) to complete. Data will be transferred immediately to an internal RedCap
7. Following completion of health questionnaires, the participant will be directed to make an appointment at their local LifeLabs using their infrastructure (contract already executed)
8. Blood sample will then be donated at LifeLabs and sent back to The Hospital for Sick Children as per below
9. Remuneration will be distributed electronically through giftcards

Inclusion/ Exclusion Criteria

Inclusion: Healthy women aged 18 to 40 years with singleton natural pregnancy.

Exclusion: Participants with a history of chronic illness or metabolic disease (including but not limited to gestational diabetes or preeclampsia/eclampsia), acute illness within the previous month, use of prescribed medication over the previous 2 weeks, use of non-prescribed medication over the past two weeks, will be excluded from this study.

Data Collection

Study participation will require: written informed consent, anthropometric measurements (height and weight), completion of a health questionnaire and small blood donation. Demographic data collected via health questionnaire will include: age, ethnicity, hours fasted, prescription use, and conception method (i.e. natural or assisted). Participation at any time point will require a post-pregnancy follow-up questionnaire via telephone to occur one month after the participant reported due date. This information is indicated on all informed consent forms and participants will only be contacted by the study team. Blood samples will be collected using serum separator (SST) and K_2EDTA tubes. Serum samples will be collected, processed within 8 hours, and aliquots frozen at -80°C until testing. Participant data will be

screened before entry into the database to ensure that only data from healthy individuals were used in the analysis.

Sample Size and Collection

Blood samples will be collected through standard venipuncture procedure according to CLSI guidelines. Samples will be collected:

I. On-site at the Hospital for Sick Children. Participants will schedule a time to visit SickKids wherein a trained phlebotomist hired by the CALIPER program will collect blood samples with informed consent.

II. Off-site at a clinic site (see description above) by a trained phlebotomist or registered nurse hired by the CALIPER program with informed consent.

III. Off-site at LifeLabs Medical Services

A total of 35.5mL (~3 tablespoons) of blood will be collected from each participant (**Table 1**). This is significantly less than the 50mL maximum recommended (45 CFR 46.110 and 21 CFR 56.110). Different collection tubes will be required as a result of specific pre-analytical requirements for biomarkers of interest (**Table 1**). Additionally, we will be recruiting pregnant women at four time points, corresponding to the three trimesters of pregnancy as well as postpartum. Thus, one individual can participate in this study up to four times (once at each time point). It is important to note that a participant can consent to participate in all or only one time point and opt out at any time (see Participant Consent Form). Thus, serial sample collection is not required for the purposes of this study. As CLSI recommends 120 individuals per partition, approximately 500 mothers at each trimester will be consented to participate in this study. This will allow for further partitioning within each trimester as well as by other potential covariates such as body mass index pre-pregnancy, ethnicity and chronological age. This will also allow for a margin for *a posteriori* exclusion following delivery based on the follow-up questionnaire call.

Table 1. Prospective maternal sample types/volume.

Time Point	Sample Size	Sample Type	Total Volume
Pregnancy: 2-13 weeks	500	1 Whole blood (K_2EDTA)	10mL
		3 Serum (SST)	25.5 mL (8.5 mL each)
Pregnancy: 14-26 weeks	500	1 Whole blood (K_2EDTA)	10mL
		3 Serum (SST)	25.5 mL (8.5 mL each)
Pregnancy: 27-35 weeks	500	1 Whole blood (K_2EDTA)	10mL
		3 Serum (SST)	25.5 mL (8.5 mL each)
Postpartum: 1-3 months	500	1 Whole blood (K_2EDTA)	10mL
		3 Serum (SST)	25.5 mL (8.5 mL each)

Phase II: *Sample Analysis for Biomarkers of Health & Disease*

Blood Testing

Specimens will be processed by experienced personnel using automated methods validated for clinical use in accredited laboratories who perform routine analysis of specimens. Specifically, as whole blood samples require immediate testing, samples will be immediately analyzed prior to centrifugation.

Conversely, serum testing does not require immediate analysis. Thus, all SST collection tubes will be centrifuged at 4000 rpm for 10 minutes, aliquoted within 4 hours of collection, and frozen at -80°C until analysis.

Table 2 indicates the biomarkers of interest as well as their associated sample volumes. These biomarkers include routine and emerging clinical indicators of health and disease (i.e. electrolytes, hepatic, endocrine, cardiac, lipid, and infection markers) in pregnancy. This panel was established based on expert consensus from several OBGYN clinicians, and clinical chemists across Canada in a Canadian Institutes of Health Research-funded in-person workshop. Furthermore, small test sample volumes for these parameters will allow a margin for dead volume as well as for the additional measurement of other clinically relevant tests, serving as a robust biobank of maternal healthy samples.

Table 2. List of biomarkers of interest for maternal and neonatal/infantile samples and their associated sample volumes based on requirements.

Maternal Biomarkers of Interest	
Biomarker	*Sample Volume*
Renal & Hepatic Markers	
Alanine Aminotransferase	5.3 µL
Albumin	1.5 µL
Alkaline Phosphatase	7.0 µL
Amylase	4.0 µL
Aspartate Aminotransferase	5.3 µL
Cystatin C	2.0 µL
Creatinine	3.6 µL
Gamma Glutamyltransferase	2.5 µL
Lactate Dehydrogenase	3.2 µL
Total Protein	4.0 µL
Urea	2.0 µL
Uric Acid	3.0 µL
Electrolytes & Metabolites	
Chloride	15 µL
Potassium	15 µL
Phosphate	2.6 µL
Sodium	15 µL
Glucose	2.0 µL
Endocrine & Adrenal Markers	
Free Thyroxine	45 µL
Free Triiodothyronine	25 µL
Thyroid Stimulating Hormone	150 µL
Prolactin	30 µL
Cortisol	20 µL
Hematology & Cardiac Markers	
Complete Blood Count	25 µL
Brain Natriuretic Peptide	100 µL
Troponin I	160 µL
Infection & Anemia-Related Markers	
C Reactive Protein	4.0 µL

Ferritin	20 µL
Iron	20 µL
Lipid & Other Markers	
Cholesterol	1.5 µL
High Density Lipoprotein	2.0 µL
Triglyceride	1.5 µL
Placental Growth Factor	50 µL
Total (32 biomarkers)	**747 µL**

All hematology parameters will be analyzed via the Sysmex-XN300 (Sysmex, Japan) platform located at The Hospital for Sick Children. Remaining parameters will be assessed via the Abbott Alinity ci (Abbott Diagnostics, Chicago, USA) chemistry and immunoassay platform located at The Hospital for Sick Children. All analytical methods will be controlled according to the manufacturer's instructions by preventive maintenance, function checks, calibration, and quality control. These methods are well-validated, efficient, and high throughput, with the potential to process 300 samples for over 20 biomarkers in under 8 hours. All platforms are currently available to research investigators. All samples tested will undergo automated interference analysis for hemolysis, icterus, and turbidity, and samples will only be included in statistical analysis when all analytical parameters are deemed acceptable.

In cases where equipment is not available, aliquots may be sent to other sites to be analyzed. De-identified samples may be shipped to collaborating organizations or industry partners for analysis. Any additional studies that may require analysis of samples outside of SickKids will be reported to the REB for approval through future amendments with the appropriate Data and Materials Transfer Agreements in place. A collaboration with Horizon Health Network (Dr. Yu Chen. NB) is currently in place to send retrospective data from their institute in pregnancy for analysis at SickKids. A RCMO has been submitted and transfer will not occur until REB amendment approval and DMTA execution.

For all studies where sample analysis occurs outside of SickKids, the following documentation will be prepared and maintained by study team;

1. REB amendment and approval
2. Completed and approved Data and Materials Transfer Agreement
3. List of sample ID numbers, number of aliquots shipped, and any other information transferred corresponding to the sample ID (e.g. age, sex, and ethnicity) will be generated. This information will be maintained by the study staff in excel spreadsheets for each collaborative study, stored in the secured CALIPER network drive, only accessible by study staff.
4. Name and contact information for study partner at collaborative site, shipping details and information for laboratory at collaborative site.

Sample Storage and Disposal

All leftover samples will be aliquoted and stored at -80°C in the Department of Clinical Biochemistry at The Hospital for Sick Children, room 3607. Samples will be stored under double lock, accessible only to designated CALIPER team members. Each aliquot will be labelled with a unique CALIPER Mother & Child ID number only, and no identifying personal information will be located on samples. Immediately following collection and prior to sample processing or analysis, requisition forms including the participant name, partial date of birth, time of collection and CALIPER Mother & Child ID will be paired with the sample. Upon sample processing, requisition forms will be removed and filed under double lock in the CALIPER office (Room 5406), separate from data collection forms/questionnaires. Newly collected

samples will be stored for up to 5 years at -80°C, or until all aliquots have been used. At the end of this 5-year period, all remaining aliquots will be deidentified/anonymized and discarded using biohazard waste bins. This is the same protocol currently used in the REB-approved CALIPER study (REB #1000010867).

Phase III: *Statistical Data Analysis*

The statistical methods for reference interval determination have been tested/validated extensively and implemented successfully in the CALIPER pediatric reference interval initiative. This study will follow identical methodology to previous CALIPER publications. Specifically, reference values for each parameter will be plotted by both chronological and gestational age and colour-coded by sex. Age- and sex-specific differences will be visually assessed and confirmed statistically using the Harris & Boyd method. This method is based on a comparison of medians and critical z score values for each partition. After partition establishment, outliers will be removed using the Tukey method twice and the adjusted Tukey method twice for Gaussian and non-Gaussian distributions, respectively. Reference intervals will then be calculated using the nonparametric approach for partitions 120 or more subjects or the robust method of Horn and Pesce for partitions with <120 and ≥40 individuals, as per CLSI recommendations (summarized in **Figure 1**). Gestational and chronological age-specific differences in laboratory reference standards will be also be assessed.

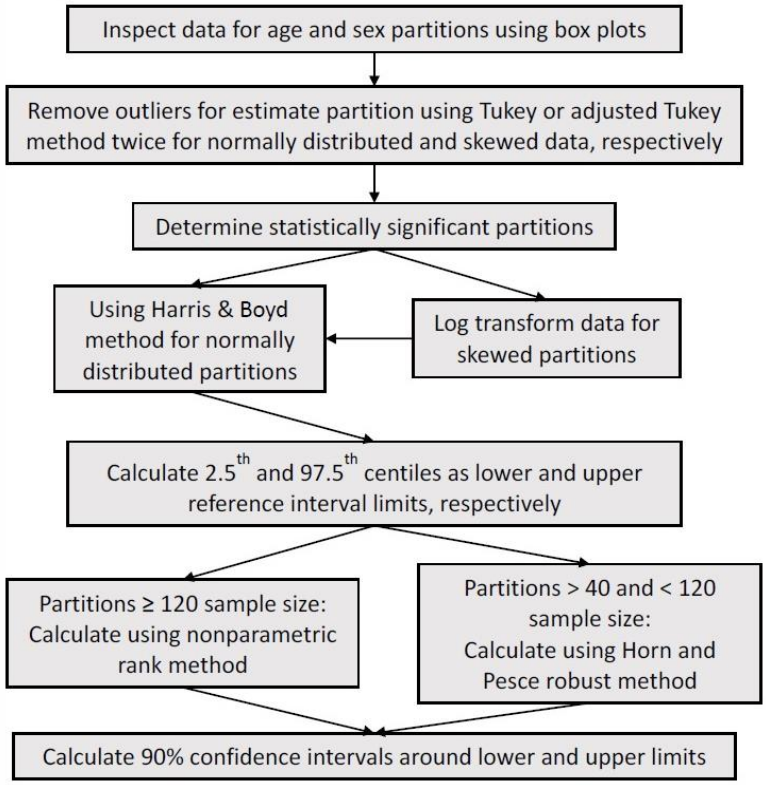

Figure 1. Schematic of general statistical approach to calculate reference intervals in CALIPER study based on a healthy reference population.

Phase IV: *Knowledge Translation*

Data generated from this study will be communicated through a multi-pronged knowledge translation approach. Specifically:

1) *Publication of several manuscripts in high-impact peer-reviewed journals*
2) *Presentation at local rounds as well as relevant national and international conferences*
3) *Development of a unique CALIPER app for pregnancy and newborns similar to the current CALIPER Web and Mobile Applications for worldwide dissemination*

CALIPER recently launched two novel e-communication tools, including a Web App (www.caliperdatabase.org) as well as a Mobile App (available on iTunes and Google Play). These web and mobile apps provide ready and free access to comprehensive pediatric reference intervals, allowing physicians to interpret laboratory test results for pediatric patients using the latest information available. These online platforms also provide an easy-to-use interface for laboratory specialists, other healthcare workers as well as patients and their families. To date, hundreds of hospitals and reference laboratories in Canada, the US and over 100 countries worldwide have already implemented use of CALIPER reference intervals in their clinical practice, improving the standard for pediatric care on a global level. The addition of accurate and robust reference intervals for pregnancy as well as neonatal and infantile periods to this existing infrastructure will facilitate maximal impact of study results.

EXPECTED TIMELINE

We expect to begin recruitment in May 2020 after obtaining SPRINT and REB approval. We anticipate to recruit maternal participants over the next 6 to 12 months, depending on initial recruitment rates, and will have preliminary data analysis completed at the one-year mark. We anticipate the entire study will take 2 years to see to completion.

ADVERSE vs. SERIOUS ADVERSE EVENT

Adverse Event: An adverse event is defined when:

- An individual is harmed during participation. This may include:
    a) severe bruising to the participant' arm after blood draw
    b) a participant fainting either before, during or after giving a blood sample; fainting may also result in bodily harm due to a fall
    c) a participant feeling ill, experiencing nausea, or vomiting
- An abnormal laboratory result is found during sample analysis
- Any other unfavourable or unintended symptom resulting from participation

Serious Adverse Event: A serious adverse event is defined when any of the above situations result in hospitalization of the participant. A serious adverse event would also include any instance when donating a blood sample results in a prolonged disability (e.g. bruising that persists longer than normal). Please note, all aspects of participation in our project are not life threatening. All events which may lead to a serious adverse event are ensured to be prevented.

Prevention of Adverse Events: Study team will take the following measures during participation to prevent the occurrence of and adverse or serious adverse event:

i. All blood draws will be performed by trained phlebotomists from the Hospital for Sick Children

ii. Phlebotomists will provide the participant with after-care advice to minimize bruising
iii. Lay-down stations and juice will be provided to minimize risk for those participants that feel dizzy/lightheaded/faint following blood collection
iv. In the very rare event that a serious adverse event occurs, where a participant requires hospitalization or attention from a physician, study staff will call 911 or transport to the nearest Emergency hospital

ETHICAL PROTOCOL

Benefits: In addition to knowing one has helped pregnant women with medical concerns across Canada, participants themselves (and/or a family member or friend) could potentially be a patient at a hospital in subsequent pregnancies and benefit directly from the results obtained from this study. The major benefit of this project will be an accurate and reliable determination of what biomarker levels are healthy/normal when a pregnant woman with medical concerns is screened for a disease. This in turn will contribute to better assessment and treatment of pregnant women at hospital centers across Canada. This will also benefit the health of mother & child. Participant laboratory test results will be available upon request via a secure platform. Remuneration will include: $20 honorarium as well as a small prenatal gift basket at each collection point.

Potential Harms: During the donation process, phlebotomists will collect a small blood sample from the participant's arm using a needle. There may be slight discomfort, bruising or redness that will usually disappear within a few days. For many participants, applying pressure with a cotton ball immediately after blood donation can help alleviate any bruising or redness. Blood donation is usually a quick process (about 3 minutes). Depending on the participant's comfort level, it can sometimes take a little longer.

How potential harms will be minimized: All phlebotomists that will be collecting blood samples are employees of The Hospital of Sick Children. All phlebotomists have met credentials and have documented previous experience. They will assist the pregnant women during the blood donation process to make them feel as comfortable as possible. Phlebotomists will also provide the participants with after-care advice to minimize any potential bruising.

Consent Forms: We have generated a participant consent form. We have also generated a study version tracking log and new study binder to ensure that only the most recent, REB approved consent and assent forms are used. All changes to consent forms will be authorized, signed and dated by the research coordinator for approval. Individuals will not participate unless their consent form has been signed and dated appropriately.

Obtaining Consent: The process for obtaining consent will vary depending on the location of the clinic/environment in which the individual will be participating. Based on the nature of the project, there are two ways pregnant women can participate in this study:

1. **At a Community Clinic:** A study coordinator will approach the head/coordinator of the organization (i.e. prenatal center, community center, OBGYN office, midwife center) and meet with them to discuss the project and answer any questions they may have. After the organization has consented to assist with promotion and recruitment for the project, an information session will be set up and/ or promotional materials will be handed out to inform the community of the project and the clinic date. Coordinator contact information will be

provided on all promotional materials, so that community members may contact the study team directly to answer any questions they may have. On the clinic day, pregnant women are welcome to participate. The project will be explained again to the participant where they have an opportunity to ask any questions prior to participating. This is the same protocol currently used in the REB-approved CALIPER study (REB #1000010867).

2. **At HSC:** Pregnant women may contact Project Coordinator directly to schedule an appointment time they can participate. Participants will be checked in by a team member where an Informed Consent Discussion form will be completed. The project will be explained again to the participant where they have an opportunity to ask any questions prior to participating. This is the same protocol currently used in the REB-approved CALIPER study (REB #1000010867).

PRIVACY AND CONFIDENTIALITY

Study Materials: Questionnaires that contain participant information will be distributed with an envelope that can be returned sealed. These questionnaires are obtained by the study coordinators. Other study team members, including volunteers, may help check in participants and review the questionnaire with them. After the participant has been checked in with a study team member at time of participation, the participant's questionnaire, consent forms, blood sample tubes will be labelled with a CALIPER Mother & Child ID code. Following the clinic, forms containing identifying information (i.e. cover page) will transcribed into the Master Linking Log and stored in a separated RedCap database. All contact forms will be destroyed, as per REB policy.

Database: The CALIPER Mother & Child ID numbers and de-identified participant information (i.e. study questionnaires answers) will be translated into a RedCap database. A separate RedCap database will be used to link CALIPER Mother & Child ID numbers to identifiable information (i.e. participant name, contact information). The Mother & Child databases will be protected in the following ways: firstly, team members must have permission to access the CALIPER shared folder based on their log-in information, and secondly, the RedCap databases are password protected, and only team members with access to the password will be able to open the online database files.

Participant Files: Each participant file will contain a cover page (contains identifying participant information), which will be destroyed upon entry to Master Linking Log & RedCap database. This cover page will include a checklist of all paper documents that should be included as part of the participant file (de-identified information- questionnaire, requisition form), and will be signed by the study team member who files the participant file and can be held responsible in case of missing documentation. All hard copies of de-identified participant information is located within the participant's file under double lock, in filing cabinets in the CALIPER office at The Hospital for Sick Children. Only the PI and coordinator have access to these cabinets.

Publications: All published results are summary statistics and are fully anonymized.

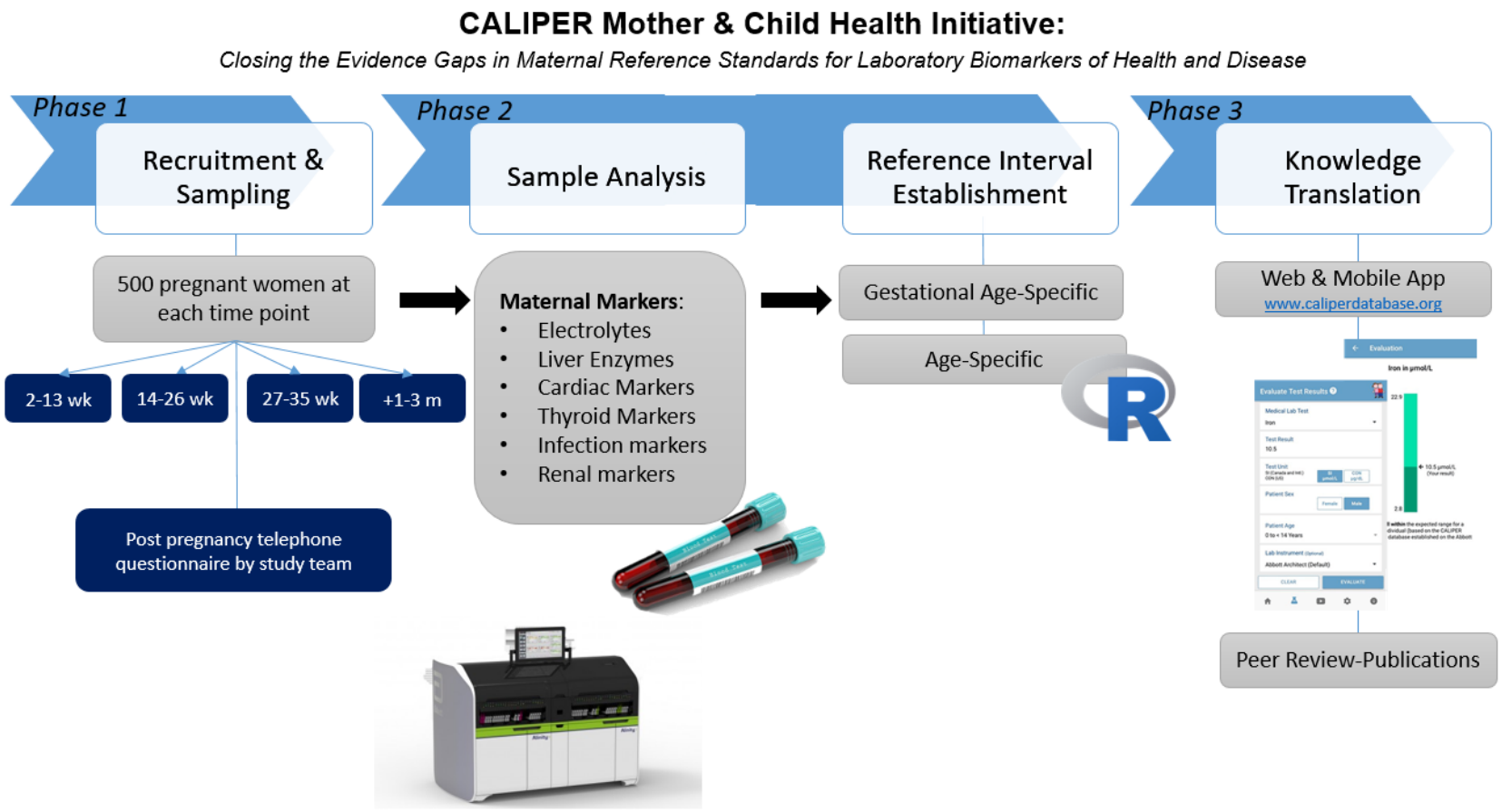

Figure 2. Overview of CALIPER Mother & Child Health Initiative study design.