HEALTHY LIFE TRAJECTORIES INITIATIVE

Data Monitoring Committee Charter

December 2020

Version 3.1

Healthy Life Trajectories Initiative (HeLTI) Data Monitoring Committee (DMC) Charter

C o n f i d e n t i a l

Name of Sponsors:	Canadian Institutes of Health Research (CIHR) National Natural Sciences Foundation (NSF) Department of Biotechnology (DBT) South African Medical Research Council (SAMRC)
Trial Registration Numbers:	China: ChiCTR1800017773 South Africa: PACTR201903750173871 Canada: http://orcid.org/0000-0002-8887-5359 India: ISRCTN20161479
Contacts at HeLTI:	HeLTI Office: Elizabeth Bojarski (Bojarski@lunenfeld.ca; helti@lunenfeld.ca)
Date of Charter:	v. 1.0: June 7, 2019; v. 1.1: June 20, 2019; v. 2.0: July 23, 2019; v. 2.1: October 24, 2019 v. 2.2: November 5, 2019 v. 2.3: November 19, 2019 v. 2.4: December 12, 2019 v. 2.5: January 21, 2020 v. 2.6: February 24, 2020 v. 2.7: March 30, 2020 v. 2.8: August 14, 2020 v. 2.9: September 4, 2020 v. 3.0: November 18, 2020 v. 3.1: December 21, 2020

Table of Contents

Confidential

This is a HeLTI document that contains confidential information. Nothing herein is to be disclosed without written consent from HeLTI.

This Charter structure was designed using 'A proposed charter for clinical trial data monitoring committees: helping them do their job well' from the DAMOCLES Study Group (Lancet 2005; 365(9460) 711-22).

1.0 Introduction

1.1 HeLTI Trials

The Healthy Life Trajectories Initiative (HeLTI) is a research collaboration of investigators from Canada, China, India and South Africa that is funded by the Canadian Institutes of Health Research (CIHR), the National Natural Science Foundation of China (NSFC), the Department of Biotechnology (DBT) India and the South African Medical Research Council (SAMRC). The World Health Organization (WHO) helped establish the collaboration and provides technical and monitoring support.

The aim of this initiative is to generate high quality evidence to inform decisions regarding policy and programs to prevent childhood obesity and to improve early childhood development. Randomized controlled trials in each of the four countries will test interventions starting in preconception and continuing in pregnancy and through early childhood to age five. Two studies are cluster randomized trials and the other two are individually randomized. Study lengths are approximately 8 years from enrollment to last participant follow-up.

The primary outcome measure in all trials is body composition of children at 5 years of age. Additional key outcomes include measures of preconception health, pregnancy outcomes, early childhood development and other anthropometric indices. There is significant harmonization across the four trials with respect to interventions and outcomes.

1.2 Scope of Charter

The purpose of this document is to describe the roles and responsibilities of the independent Data Monitoring Committee (DMC) for the HeLTI trials, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings and the relationships with other groups and committees. This Charter will outline the roles and responsibilities of the DMC and serve as the Standard Operating Procedures (SOP).

2.0 Roles and Responsibilities

2.1 Overall Aims

The objective of this committee is safeguarding the interests of study participants and assuring the integrity and credibility of the HeLTI trials. Based on cumulative reports prepared for the DMC and DMC Open Session discussions, the DMC will evaluate safety, study conduct, scientific validity and data completeness of the study. The members of the DMC serve in an individual capacity and provide their expertise and recommendations.

2.2 Terms of Reference

The DMC provides independent recommendations to the Trial Executive Committee on the continuing scientific validity and safety of the trials and the intervention under investigation. The DMC will have the responsibility of assuring that participants are not being exposed to unnecessary or unreasonable risks as a result of the pursuit of the study's scientific objectives and their participation in the trial. In addition, the DMC will review the quality of the trial protocol, implementation, data, and any other factors affecting the scientific validity of the trial.

2.3 Specific Roles of DMC

The DMC will review the study protocols and any protocol deviations in relation to the safety of participants and the overall scientific integrity and credibility of the trials. Recommendations will be directed to the Chairs of the Trial Executive Committee of the respective trial and to the HeLTI Research Committee (copied as a courtesy to ensure the flow of information). The DMC will monitor the quality and performance of the trials, safety of participants, and will review efficiency data based on tables and

reports provided in the Appendix section. Tables will be completed by a local statistician nominated by the local Trial Executive. Feedback will be sought from the DMC prior to submitting a final report for assessment. DMC may use reporting template (Illustrative report for DMC to Chairs of Trial Executive Committee, page 36) provided in the Appendix section to forward their recommendation(s) to the Chairs of the Trial Executive Committee and Research Commitee. There is no planned formal interim analysis, except reporting on SAEs. The main responsibility of the DMC will be to monitor progress of the trials and to ensure safety.

Monitoring of **quality and performance** of the study will include reviewing patient recruitment, flow of forms, loss to follow-up, missing data on key outcomes, quality control of the data, adherence to protocol (in consideration of an adaptive design) and appropriateness of protocol changes with regard to scientific objectives.
Monitoring of **safety** (adverse events) will include reviewing risk of harm inherent in participating in the study, and the effect of protocol changes on risk (see Appendix 1). All SAEs will be reported to local ethics boards within 15 calendar days of the local site Principal Investigator becoming aware of them. Any possibly related unexpected SAE or related unexpected SAE will be reported to the DMC Chair within 15 calendar days of the local site Principal Investigator becoming aware of them. Any fatal serious adverse events (SAEs) require expedited reporting to local ethics boards within 7 days of event being reported to the local site Principal Investigator (see Appendix 1 for additional detail). Any fatal possibly related unexpected SAE or fatal related unexpected SAE will be reported to the DMC Chair within 15 calendar days of the local site Principal Investigator becoming aware of them. Ad-hoc follow-up meetings between the local Chairs of Trial Executive Committee and the DMC can be convened to address additional concerns (i.e. unusual frequency of SAEs), if needed. Importantly, local trial teams can refer any SAE event of concern to the DMC Chair for DMC consideration.

Reports will be provided to the DMC at 12-month intervals. As there are four large HeLTI trials, each conducted in their own countries (Canada, China, India and South Africa), for efficiency, the DMC will be provided access to country-specific statisticians to assist in preparation of DMC reports. Monitoring of progress, recruitment, follow-up and data quality will be conducted. Harmonization of trials will not be assessed.

3.0 Early in the Trial

3.1 Input

Before recruitment begins, the trials have undergone review by the funders, scrutiny by other trial committees and research ethics boards (REB). DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trials.
The DMC will meet before two of the four trials commence and during the very early stages of the other two trials to discuss protocols, analysis plans, future meetings and to have the opportunity to finalize the Charter directly with the Principal Investigators. At this first meeting, proposed tables will be used to familiarize the DMC members with the format that will be used in the reports.

3.2 Agreement

Once discussed, each DMC member can formally include their assent by confirming that they agree to: (1) be part of the HeLTI DMC, (2) the contents of this Charter and (3) treat all sensitive trial data and discussions confidentially.

4.0 Composition

4.1 Membership

The HeLTI Research Committee, comprised of two Principal Investigators from each of the four HeLTI trials (Canada, China, India and South Africa) have selected 5 members to comprise a central independent DMC that will monitor the four trials. The members will have appropriate clinical expertise (in areas of statistics, nutrition, obstetrics, child health and development) and knowledge about the design, monitoring and analysis of clinical trials necessary to conduct ethical and scientifically rigorous studies.

Members will be appointed by consensus of the HeLTI Research Committee. Principal or co-Investigators in any of the four HeLTI studies will not be eligible for DMC membership to ensure there is no conflict of interest.

In addition, because real or perceived conflicts of interest (CI) can be detrimental to the integrity of the DMC process, CI should be properly disclosed and carefully addressed prior to and during the DMC process. The following conflict of interests should preclude membership on the DMC: ownership of stock in affected companies supplying resources for the trials; having a leadership role in the scientific development of the interventions being evaluated by the trials; potential involvement in the clinical care of trial participants; or potential to have regulatory or other oversight responsibilities for the trial interventions being investigated. Certain other activities, such as service on multiple DMCs of competing interventions or even time-limited consulting agreements on issues not related to the ongoing trials, either with the trials' sponsor(s) or with competitors having related interventions, typically would not constitute unacceptable conflicts of interest, but members should report such arrangements annually, or whenever a new potential conflict arises, to the DMC Chair. Appendix 2 has the agreement and potential competing interests form.

The members of the DMC for the four HeLTI trials are (see Appendix 3 for members' details):

1. Ashish Bavdekar
2. Dean Fergusson
3. Muhammad Mamdani
4. Fangbiao Tao
5. James Walker

4.2 DMC Chair

The Chair should have previous experience serving on DMCs, experience of chairing meetings and should be able to facilitate and summarize discussions. The HeLTI Research Committee will appoint one of the selected DMC members as Chair of the DMC, based on recommendations by the DMC members. The Chair will serve as the primary contact person for the DMC and ensure those involved in the day-to-day management of the study are excluded from DMC voting procedures. The DMC Chair is James Walker.

4.3 Responsibilities of HeLTI Research Committee, the Trial Executive Committee and the HeLTI Office or their designee(s)

The HeLTI Research Committee approves the selection of the DMC Chair and members and reviews and approves the DMC Charter. Each Trial Executive Committees reviews and implements the DMC recommendation(s), as appropriate; and advises appropriate individuals of DMC recommendations and notifies regulatory authorities, other agencies, and co-Investigators, when required or necessary.

The HeLTI Office collects the reports from each of the trials, ensures that the DMC Chair and his designate receive the reports via email and schedules and organizes DMC meetings on annual basis or as

frequently as needed. The DMC Chair will send recommendation to the Chairs of the Research Committee and the Chairs of the respective Trial Executive Committees.

5.0 Relationships

5.1 Relationships with Committees

Acting in an advisory role to the Trial Executive Committees, the Trial Executive Committees will consider all recommendations received by the DMC and take action(s) accordingly.

5.2 Payments

An honorarium of $1,000 CAD will be provided to each member of the DMC for every in-person meeting attended (expected every 12-18 months) for the term duration of five years. All economy travel and accommodation costs will be reimbursed by the HeLTI Office, with appropriate documentation and abiding by institution (Sinai Health System) guidelines (see Appendix 4).

6.0 Organization of DMC Meetings

6.1 Expected Frequency and Location

The exact frequency of meetings will depend upon any statistical plans specified, and otherwise on trial events. The wishes of the DMC and needs of the Research Committee will be considered when planning each meeting. The intent is to meet every 12-18 months, with the preference to the shorter (12 months) period. The DMC meeting venues will be arranged by the HeLTI Office in collaboration with the DMC and the Statistical Analysis Centers of the four trials. Locations for in-person meetings will be chosen for ease of access rather than attractiveness of venue. Socializing between the DMC and the HeLTI Research Committee at dinners and functions held in advance or after the DMC meetings is discouraged as it is seen as being too collegial a relationship between the DMC and RC.

6.2 Meeting Structure

The initial meeting will be via teleconference for introductions, to nominate a Chair of the DMC, provide feedback on the draft DMC Charter and to discuss dates for an in-person meeting. During subsequent meetings, the DMC will consider information, proposals and questions presented by the study investigators. After review of the periodic reports, the DMC may ask for clarification or additional information from the HeLTI Research Committee or country-specific HeLTI trial teams.
Both open and closed sessions will occur. Closed sessions will include only DMC members and others whom they specifically invite (e.g. trial statistician(s)). In open sessions, all those attending the closed session are joined by the PI(s), and/or the HeLTI Office. The general format of the meetings will be as follows:

1. Open session: Introduction and any ‘open’ parts of the report
2. Closed session: DMC discussion of ‘closed’ parts of the report and, if necessary,

Each meeting will include a recommendation to continue or terminate the study and whether the DMC has any concerns about participant safety made by a formal DMC majority or unanimous vote. Should the DMC decide to issue a termination recommendation, the full vote of the DMC is required. In the event of a split vote, majority vote will rule and minority report should be appended.

6.3 DMC Reports

Open Session Reports – Open session reports will be discussed in the open meeting and will include administrative reports by site that describe participants screened, enrolled, completed, and discontinued (including reasons). Demographic and key baseline characteristics of the study population

will be described. A summary of safety issues (adverse events and serious adverse events) as well as any other information requested by the DMC may also be in the open session report (see Appendix 5). The DMC may direct additions and modifications to the reports on a one-time or continuing basis.

Closed Session Reports – Closed session reports will be prepared by local statisticians and will include the same information as presented in the open session but broken down by intervention group, in addition to supplemental data and/or material. Printed copies of the closed reports should be destroyed immediately following the meeting.

7.0 Trial Documentation and Procedures to Ensure Confidentiality and Proper Communication

Closed sessions: In addition to all the material available in the open session, the closed session material will include efficacy and safety data by arm for each trial. Blinded data will be presented.
The people who will see the accumulating data and interim analysis will be local statisticians and the Trial Executive Committee. DMC members do not have the right to share confidential information with anyone outside the DMC, including the PIs. There will be no sharing of trial data (meta-analysis) without the consent of the HeLTI Research Committee. The DMC will inform the HeLTI Research Committee if there is a plan to combine data from different trials.
The DMC will report its recommendations in writing to the Chairs of the Trial Executive Committee and and the HeLTI Research Committee. A letter with the recommended decision on the continuity of the trial will accompany the report. If the trial is to continue largely unchanged, then it is often useful to include a summary paragraph suitable for trial promotion purposes. An example of such a letter is provided in Appendix 6.
After each meeting, confidential papers, letters and reports should be destroyed by DMC members. New copies of previous reports will be circulated with the latest report before each meeting. After the final report has been submitted, DMC members should destroy all interim reports (paper and electronic).

8.0 Decision Making

8.1 Possible Recommendations

Trial decisions will be based on individual country data and associated trials. A decision in one country does not necessarily pertain to that of another country.
Decisions or recommendations open to the DMC for each trial include, but are not limited to:

- No action needed, trial continues as planned.
- Early stopping due to futility.
- Stopping certain aspects of the intervention (e.g. micronutrient).
- Extending recruitment or extending follow-up.
- Stopping a single arm of a multi-arm trial.
- Sanctioning and/or proposing protocol changes.

8.2 Previous HeLTI 'Unblinding' Discussion

In 2018, the HeLTI Research Committee sought feedback from external experts in clinical trials, epidemiology, statistics, ethics and DOHaD science about the unblinding of results to investigate interim analyses. After consideration of this feedback and extensive further discussion, the HeLTI Research Committee had resolved to unblind at different times of the trials, to investigate interim analyses at the end of each of the four phases (preconception; pregnancy; infancy (0-2 years); and early childhood (3-5

years)). However, in order to protect the reporting of the primary outcomes, these analyses will be declared a priori as part of the analysis plans.

8.3 Reaching Decisions

In its deliberations, the DMC will attempt to reach a consensus before making any recommendation. If possible, every effort should be made for the DMC to reach a unanimous decision. The DMC will carefully weigh all information available and give due consideration to the ongoing balance between risk to the participant and possible participant benefits. When this balance is not clear, or when there is persistent uncertainty or doubt, the DMC recommendations are to reflect the principle that human safety takes precedence over trial objectives. It is important that the implications (ethical, statistical, practical, financial) for the trials are considered before any recommendation is made. Recommendations made to the investigative team (Chairs of the Trial Executive Committee) should represent the collective judgment of the DMC and reflect all information available to the DMC at the time the recommendations are made.

There should be a minimum number of three attendees before the DMC is quorate for decision making. If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC Chair for consideration during the upcoming discussions.

8.4 Missing Meetings

If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they will be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they will be replaced.

9.0 Reporting

The recommendations of the DMC should be made to the Chairs of the Trial Executive Committee, usually within 3 weeks of the latest meeting. The details of the meeting (separate for open and closed sessions) should be recorded. The DMC Chair should sign off on any minutes or notes.

A formal report containing detailed suggestions and recommendations about the trial will be prepared by the DMC Chair. The draft report will be sent to the other DMC members for review and approval. Once approved by all DMC members, the DMC Chair will forward the final report to the Chairs of the Trial Executive Committee, with copies sent to the HeLTI Research Committee and the HeLTI Office.

If accepted by the Chairs of the Trial Executive Committee, the Chair will circulate the DMC's recommendation to the Research Ethics Boards.

The DMC will not report directly to the Study Sponsors, but rather will convey recommendations through the Chairs of the Research Committee and Chairs of the Trial Executive Committee. In the event of a DMC recommendation to terminate one arm of the trial or the trial entirely, the DMC will provide their recommendation and rationale to the Chairs of the Research Committee and Chairs of the Trial Executive Committee. The Chairs of the Research Committee will forward the letter(s) with the recommended decisions regarding the continuity, or not, of the trial to the Sponsors (example of such letter is provided in Appendix 6).

If disagreement between the DMC's recommendation(s) and the Trial Executive Committee's decision, a further committee may be convened to adjudicate (external experts, who are not involved with the trials). In the event that the Trial Executive Committee disagrees with the DMC recommendation(s) to modify to terminate the trial, a third-party arbitrator group may be called upon.

The HeLTI Research Committee and relevant Research Ethics Boards must be immediately notified if this situation arises. A third-party group will be convened, with requisite knowledge and experience to make a final decision in the matter. The selection of the third-party arbitrator group will be made by mutual consent of both the Trial Executive Committee and the Chair of the DMC (e.g. WHO Public Health Reference Group). It is the responsibility of the Chairs of the Trial Executive Committee to notify the appropriate Research Ethics Boards of any recommendation to stop the trial.

10.0 After the Trial

At the end of the trials, there will be a meeting to allow the DMC to discuss the final data with the Chairs of the Trial Executive Committee and HeLTI Research Committees and give advice about data interpretation. Copies of the Open of the DMC will be provided to the Chairs of the Trial Executive Committee at the completion and publication of the trials. Copies of the Closed Session Minutes of the DMC may be provided at the completion and publication of the trials if all DMC members are in agreement.

10.1 Publications

The DMC will be provided with a statement that the trial results will be published in an accurate and timely manner. DMC members will be named and their affiliation listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings should be included in the body of this paper. It should be specified when the DMC members may discuss issues from their involvement in the trial, e.g. 12 months after the primary trial results have been published, or when permission is agreed with the HeLTI Research Committee.

11.0 Appendices

Appendix 1: Assessment of Adverse Events in HeLTI studies

1.1 Principles:

Behavioral intervention research has lagged behind biomedical research in developing principles for defining, categorizing, identifying, reporting, and monitoring adverse events and unanticipated problems. Guiding principles used in The Brief Strategic Family Therapy (BSFT™) Effectiveness Study (Clinical Trials 2010; 7(1) 58-68) was used as a framework to consider for defining AEs in HeLTI.

(1) AEs should be grounded in previous research on the clinical population.
(2) AEs reporting should be limited to outcomes where there is plausible evidence of an association with the interventions being tested. As regards to events that are relatively frequent in pregnancy and birth cohorts (preterm birth, preeclampsia, gestational diabetes) but where there is limited or no evidence of an association with the health promotion intervention under study, and where any judgement regarding the presence of an association with the study intervention can only be based on the accumulated data from a large number of patients, the DMC will be provided, according to a preestablish schedule, tabulated reports on the incidence of these outcomes.
(3) Health Promotion Interventions could, unintentionally, lead to increased stress in some participants. Severe forms of psychosocial stress such as severe depression and anxiety are reportable Advise Events.
(4) Regarding the other reportable adverse events that have been specified, those reporting the event should attempt to assess the relatedness between interventions and AEs.
(5) Systematic monitoring is essential for identifying unexpected events.
(6) Effective monitoring is a shared responsibility (e.g. stakeholder, sponsor, DMC, REB).

1.2 Adverse Events

An adverse event is any untoward medical occurrence in subjects exposed to medical or behavioural interventions. The event does not necessarily need to have a causal relationship with the intervention. **Adverse events** will be assessed and graded according to the following:

Expected/Anticipated	Identified in nature, severity, or frequency in the current protocol, informed consent, or with other current risk information.
Unexpected/Unanticipated	Not identified in nature, severity, or frequency in the current protocol, informed consent, or with other current risk information.
Serious adverse events	Results in death; Is life threatening; Results in persistent or significant disability/incapacity; or Causes a congenital anomaly/birth defect.

Causality: Adverse events will be attributed to the following:

Unrelated	There is not a reasonable possibility that the adverse event may have been caused the intervention.
Possibly Related	The adverse event may have been caused by the intervention; however, there is insufficient information to determine the likelihood of this possibility.
Related	There is a reasonable possibility that the adverse event may have been caused by the intervention. (suspicion is enough)

Sites must report all adverse events experienced by participants that meet all three conditions: **1) unexpected, 2) related or possibly related, 3) serious.** Sites must report these to their Research ethics boards within 15 calendar days of the principal investigator becoming aware of them if non-fatal, or within 7 calendar days of the principal investigator becoming aware of them if the SAE is fatal.

All possibly related unexpected SAEs or related unexpected SAEs will be reported to the DMC Chair within 15 calendar days of the principal investigator becoming aware of them.

The following SAEs (Table 1) will be collated by each HELTI team by study allocation group (intervention vs control), and submitted to the DMC in advance of the scheduled DMC meetings (once a year):

Table 1. Reportable Serious (Severe) Adverse Events

REPORTABLE SERIOUS (Severe) ADVERSE EVENTS	Definitions
Death	
Mother's death	
Child's death	
Stillbirth Neonatal Death	Stillbirth: Defined as birth of an infant that has died in the womb (strictly, after having survived through at least the first 28 weeks of pregnancy, earlier instances being regarded as abortion or miscarriage). Neonatal death: defined as death of a live born infant within the first 28 days after birth.
Persistent/significant disability/incapacity	
Is Life-threatening	
Maternal/Child ICU admission	Defined as admission in intensive care unit (adult or child) that was not transitory and lasted more than one hour.
Congenital anomaly/ birth defect	

Table 2. Reportable Adverse Events

REPORTABLE ADVERSE EVENTS	Definitions
Child protective services involvement (voluntary or involuntary)	A set of government and private services designed to protect children and encourage family stability. The main aim of these services is to safeguard children from abuse and neglect.
Maternal/Child hospitalization	Defined as hospitalization >24 hours
Suicidal behaviour	Suicidal behaviours include any risk of attempt to inflict serious harm to self that may result in death.
Physical or sexual assault	**A Physical Assault** is the act of inflicting physical harm or unwanted physical contact upon a person or, in some specific legal definitions, a threat or attempt to commit such an action. **Sexual Assault** is defined as an assault of a sexual nature that violates the sexual integrity of the victim.
Homicidal behaviour	Any attempt to seriously injure or kill another person or ideations that represent a realistic threat to another person.

Table 3. Reportable Pregnancy and Child Events where Plausibility of Relationship to the Intervention Is Low

REPORTABLE PREGNANY AND CHILD EVENTS where plausibility of relationship to the intervention is low and do not require an event form completion	Definitions
Severe preeclampsia	Hypertension diagnosis based SBP equal to or greater than 160 mm Hg and/or DBP equal to or greater than 110 mm Hg, at gestational age equal to or greater than 20 weeks. PLUS proteinuria or maternal complications (including disseminated intravascular coagulation, pulmonary edema, convulsions–eclampsia, transfusion, elevated liver enzyme levels, platelet count < 50 × 10E9/L) defines **preeclampsia.**
Eclampsia	**Eclampsia** refers to the occurrence of new-onset, generalized, tonic-clonic seizures or coma in a woman with preeclampsia. It is the convulsive manifestation of preeclampsia and one of several clinical manifestations at the severe end of the preeclampsia spectrum.

HELLP	**HELLP syndrome:** is a life-threatening liver disorder thought to be a type of severe pre-eclampsia. It is characterized by Hemolysis (destruction of red blood cells), Elevated Liver enzymes (which indicate liver damage), and Low Platelet count.
Gestational diabetes	Is a type of diabetes that is first seen in a pregnant woman who did not have diabetes before she was pregnant and who occurs during the second or third trimester of pregnancy
Placental abruption	Early separation of a placenta from the lining of the uterus before completion of the second stage of labour
Preterm birth <28 weeks Preterm birth 28-31 weeks Preterm birth 32-36 weeks	
Baby NICU admission	Defined as admission in intensive care unit (adult or child) that was not transitory and lasted more than one hour
Severe depression	Severe depression resulting in hospitalization; EPDS score >12; PHQ-9 >10
Severe anxiety	Severe anxiety resulting in hospitalization; GAD-7 Score ≥ 15

In addition, according to a pre-agreed schedule, each study team will periodically report on the above reportable adverse events and on the following outcomes of interest according to masked study group (group A, group B) in tabular format: recruitment rates (overall and by cluster, when applicable); baseline socio-demographic population characteristics; retention rates, withdrawals (complete and partial), loss to follow-up; indicators of compliance to study intervention; indicators of data completeness; health-related outcome measures: pregnancy rates (among preconception participants); spontaneous abortion rates; voluntary abortions; preterm births (≤28 wks; 34 wks; 37 wks); hypertensive disorders of pregnancy (gestational hypertension, preeclampsia – mild, severe, HeLLP syndrome); placental abruption.

Appendix 2: Agreement and Potential Competing Interests Form

Healthy Life Trajectories Initiative (HeLTI)

Please complete the following document and return to the HeLTI Office (Bojarski@lunenfeld.ca or helti@lunenfeld.ca).

(please initial box to agree)

☐ I have read and understood the DMC Charter version

☐ I agree to join the DMC for this trial

☐ I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interests should be disclosed via the HeLTI Office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC. **Table 1** lists potential competing interests.

☐ No, I have no competing interests to declare

☐ Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests

- Ownership of stock in affected companies;
- Having a leadership role in the scientific development of the interventions being evaluated by the trials;
- Potential involvement in the clinical care of participants; or
- Potential to have regulatory or other oversight responsibilities for the trial interventions being investigated

Appendix 3: DMC Membership List

Ashish Bavdekar - Professor Ashish Bavdekar is a Pediatric Gastroenterologist at KEM Hospital and a Consultant in Pediatric Research at the KEM Hospital Research Centre in Pune, India. He completed his medical studies from B.J. Medical College, Pune and subsequently received Gastroenterology, Hepatology and Nutrition training at Sheffield Children's Hospital, and Birmingham Children's Hospital, UK. He has also been trained in Epidemiology and Biostatistics at Johns Hopkins University, USA. He is the past President of the Indian Academy of Pediatrics (IAP) – Gastroenterology Chapter and has served on several IAP task forces - Safe Injection Practices, Childhood Obesity, Neonatal Jaundice, Acute Diarrhea & Acute Liver Failure. He is a member of the Global Burden of Disease India Maternal and Child Health Expert Group, ICMR childhood anemia task force, DBT expert group on vaccine research and development. His special interests are metabolic liver diseases, pediatric nutrition, DOHAD research, gut microbiome and infectious disease epidemiology.

Dean A. Fergusson - Dean Fergusson, PhD is a Senior Scientist and Director of the Clinical Epidemiology Program (CEP) at the Ottawa Hospital Research Institute and a Full Professor in the Department of Medicine with cross-appointments to the School of Epidemiology & Public Health and the Department of Surgery at the University of Ottawa. His two areas of research scholarship are: 1) transfusion medicine and transfusion alternatives; and 2) innovative methodological research into the design and analysis of clinical trials. His methodological work in clinical trials includes the areas of clinical equipoise, innovative pragmatic trials, patient and public engagement, post-randomization exclusions, ethical use of placebo controls, and statistical approaches. He has served or chaired CIHR panels (RCT, New Investigator, Mentoring) and is an active member on editorial boards (Transfusion Medicine Reviews, Transfusion Medicine, Clinical Trials, Trials). He has also been an active member of renowned disease clinical trial networks in transfusion, critical care, and thrombosis.

Muhammad Mamdani - Dr. Mamdani is the Founding Director of the Li Ka Shing Centre for Healthcare Analytics Research and Training (LKS-CHART) of the Li Ka Shing Knowledge Institute of St. Michael's Hospital in Toronto. The LKS-CHART bridges advanced analytics including machine learning with clinical and management decision making to improve patient outcomes and hospital efficiency. Dr. Mamdani is also Professor in the Department of Medicine of the Faculty of Medicine, the Leslie Dan Faculty of Pharmacy, and the Institute of Health Policy, Management and Evaluation of the Dalla Lana Faculty of Public Health. He is also adjunct Senior Scientist at the Institute for Clinical Evaluative Sciences (ICES). Dr. Mamdani also is a member of the Human Drug Advisory Panel of the Patented Medicine Prices Review Board (PMPRB) and founded the Ontario Drug Policy Research Network (ODPRN) in 2008, which is among the world's most impactful collaborations between researchers and drug policy decision-makers. Prior to his position at the LKS-CHART, Dr. Mamdani was the Founding Director of the Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, which is Toronto's leading academic research organization focused on the design and implementation of multicentre clinical research initiatives. In 2010, Dr. Mamdani was named among Canada's Top 40 under 40. Prior to joining the Li Ka Shing Knowledge Institute and St. Michael's Hospital, Dr. Mamdani was a Director of Outcomes Research at Pfizer Global Pharmaceuticals in New York. Dr. Mamdani's research interests include pharmacoepidemiology, pharmacoeconomics, and drug policy. He has published over 450 research studies in peer-reviewed medical journals, including leading journals such as the New England Journal of Medicine, the Lancet, the Journal of the American Medical Association, the British Medical Journal, and Annals of Internal Medicine. His research has been cited over 19,000 times. Dr.

Mamdani obtained a Doctor of Pharmacy degree (PharmD) from the University of Michigan (Ann Arbor) in 1995 and subsequently completed a fellowship in pharmacoeconomics and outcomes research at the Detroit Medical Center in 1997. During his fellowship, Dr. Mamdani obtained a Master of Arts degree in Economics from Wayne State University in Detroit, Michigan. He then completed a Master of Public Health degree from Harvard University in 1998 with a concentration in quantitative methods, focusing on biostatistics and epidemiological principles.

Fangbiao Tao – Fangbiao Tao, PhD is a professor in the Department of Maternal, Child & Adolescent Health, School of Public Health at Anhui Medical University, China. His research interests focus on: 1) environmental exposure in early life and child health; and 2) adolescent developmental and behavioral health. Professor Tao pioneered the large-scale, prospective and community-based cohort study in China. This birth cohort study was designed to examine the associations between maternal environmental exposures and children's health, development and the fetal origins of adult disease. Tao's research team also implemented the annual national surveillance for adolescent behavior and health across 8-13 provinces (autonomous regions) in China, with measures on physical activity, tobacco use, sleep, screen time and excessive internet use, diet behavior, depression, anxiety, social communication and other psychological problems, early puberty timing, overweight and obesity, among others.

James Walker

Professor James (Jimmy) Walker is a clinical academic at the University of Leeds in the UK specialising in high risk obstetrics. His particular interest is in pre-eclampsia. He has 35 years of experience in clinical trials, implementation and guideline development. As Senior Vice-President of the Royal College of Obstetricians & Gynaecologists, he had a remit of global health starting initiatives in practical training and care development in the under-resourced world. This included UK volunteers travelling into country and local trainees travelling to the UK for training programs.

Prof Walker has been the Co-PI in multicentre international studies, SCOPE and Interpregen, and has experience in big data handling, the governance processes and evaluation of outcomes. He chaired the DMC of the Each Baby Counts program in maternity incidents in the UK. He chaired the Maternal mortality confidential Enquiries and now is Clinical Director of Maternity Investigations for England, with a strong emphasis on learning and patient safety.

Appendix 4: Reimbursement Guidelines

Sinai Health System's (Toronto, ON) reimbursement guidelines will be used to process reimbursement requests. This 14-page internal Sinai Health System document can be provided upon request.
For questions or additional information, please contact the HeLTI Office.
(Email: Bojarski@lunenfeld.ca; or helti@lunenfeld.ca)

Appendix 5: HeLTI DMC Report Template

HeLTI DMC Report Template
[Trial Name]
[Trial Location]

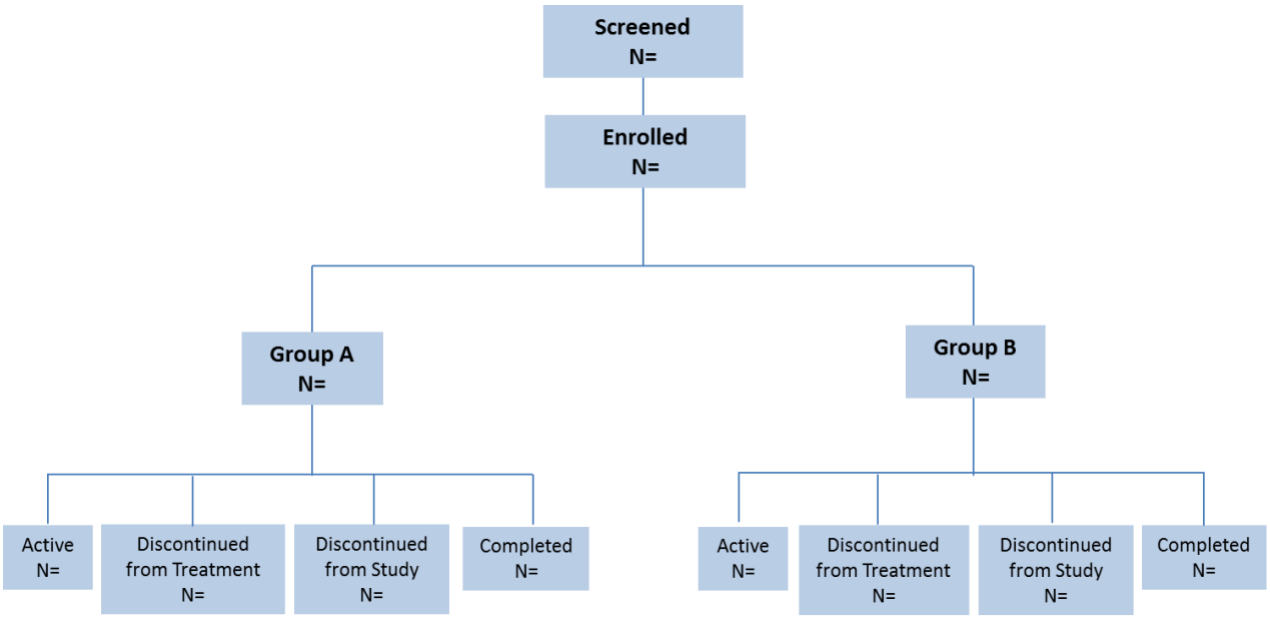
Meeting Date:
Date of Data Extraction:

Protocol Synopsis

Protocol Title	
Principal Investigator(s)	
Study Sites	
Study Activation Date	
Planned Accrual	
Planned Accrual Period	
Planned Duration	
Study Design	
Study Objectives	
Intervention Description	
Inclusion Criteria	
Exclusion Criteria	
Study Outcomes	
Study Stopping Rules	

Recruitment and Participant Status

Figure 1a. Overall Study Status



Definitions

The interim analysis includes all groups with the exception of withdrawals.
Completed (exit study) = End of study + miscarriages + twin pregnancy + participants who failed to become pregnant
Discontinued from study = Withdrawal + lost to follow up
Discontinued from treatment = Ended the intervention but pursue the cohort follow-up
List of reasons for discontinuation of the study (include table)

Table 1a*: Retention in Trial by Group According to Time of Recruitment

	Active	Lost to follow-up	End of study	Withdrawals
Group A				
Pregnancy				
Group B				
Pregnancy				

* Table to be adapted for each cohort

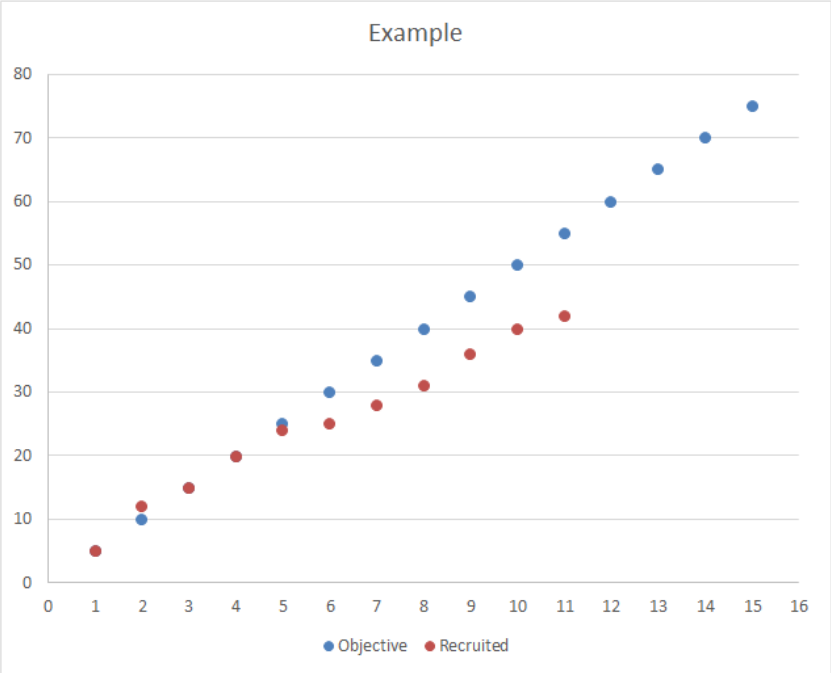
Table 2a*: Distribution of Recruitment by Study Group, by Period of Recruitment (Preconception – Pregnancy), and by Cluster

CLUSTER #	GROUP A		GROUP B	
	PC N (% target)	PG N (% target)	PC N (% target)	PG N (% target)
1				
2				
3				
……				
Number of pregnancies				

PC = Preconception PG = Pregnancy

***** The Table 2a is only applicable for HeLTI China and HeLTI India
Note: "Group C" column to be added by HeLTI India.

Figure 2a: Cumulative Recruitment by by Study Group



* Additional figures to be provided by PC and PG status for HeLTI China.

Table 3a. Demographic and Key Baseline Characteristics

Baseline Characteristics of Women Recruited in the Study	**Group A**	**Group B**
Number of women enrolled in the study		
Age		
Mean (SD)		
Range		
Maternal BMI		
Mean (SD)		
Range		
Employment Status n (%)		
Smoking status		
Education Level		
Education completed (Years)		
Mean (SD)		
Range		
Highest level of education n (%)		
Maternal Overweight (%)		
Maternal Obese (%)		
Depressive symptoms (% with EPDS score >12 OR PHQ-9 >10)		
Anxiety Symptoms (% with GAD Score >=15)		
Existing Diseases		
Diabetes n (%)		
Hypertension n (%)		
Other diseases n (%)		
Number of partners recruited (N)		

Note:

1. HeLTI China to include a global table and a specific table for PC and PG.
2. Note: “Group C” column to be added by HeLTI India.
3. Each cohort to include section with definitions of variables before/after tables.

Table 4: Adherence to Protocol for Data Collection Visits among Overall Participants Active at Visit Timepoint

Visits *	Active	Expected visits	Completed visits	Visits completed over expected %	Visits completed within time window	% of Visits completed within time window
Preconception V1						
Preconception V2						
Preconception V3						
Preconception V4						
Pregnancy V1						
Pregnancy V2						
Pregnancy V3						
Delivery						
Postnatal visit 6wk						
Postnatal visit 3m						
Postnatal visit 6m						
Postnatal visit 12m						
Postnatal visit 24m						
Postnatal visit 36m						
Postnatal visit 48m						
Postnatal visit 60m						

* "Visits" column to be adapted to cohort-specific study protocol
Note: This is a combined table for Group A and B (and C for HeLTI India) re monitoring cohort visit intervention.

Table 4a - Group A: Adherence to Protocol for Data Collection Visits among Participants Active at Visit Timepoint – Group A

Visits *	Active	Expected visits	Completed visits	Visits completed over expected %	Visits completed within time window	% of Visits completed within time window
Preconception V1						
Preconception V2						
Preconception V3						
Preconception V4						
Pregnancy V1						
Pregnancy V2						
Pregnancy V3						
Delivery						
Postnatal visit 6wk						
Postnatal visit 3m						
Postnatal visit 6m						
Postnatal visit 12m						
Postnatal visit 24m						
Postnatal visit 36m						
Postnatal visit 48m						
Postnatal visit 60m						

* “Visits” column to be adapted to cohort-specific study protocol
Note: This is a table for Group A.

Table 4b - Group B: Adherence to Protocol for Data Collection Visits among Participants Active at Visit Timepoint – Group B

Visits *	Active	Expected visits	Completed visits	Visits completed over expected %	Visits completed within time window	% of Visits completed within time window
Preconception V1						
Preconception V2						
Preconception V3						
Preconception V4						
Pregnancy V1						
Pregnancy V2						
Pregnancy V3						
Delivery						
Postnatal visit 6wk						
Postnatal visit 3m						
Postnatal visit 6m						
Postnatal visit 12m						
Postnatal visit 24m						
Postnatal visit 36m						
Postnatal visit 48m						
Postnatal visit 60m						

* “Visits” column to be adapted to cohort-specific study protocol
Note: This is a table for Group B.

Table 5a.* **Data Collection Visits:** Number of Queries

Visits	**Number of queries generated**	**Number of queries resolved and closed**	**Average time of resolution**	**% Queries unresolved**
Preconception V1				
Preconception V2				
Preconception V 3				
Preconception V 4				
Pregnancy V1				
Pregnancy V2				
Pregnancy V3				
Delivery				
Postnatal visit 6wk				
Postnatal visit 3m				
Postnatal visit 6m				
Postnatal visit 12m				
Postnatal visit 24m				
Postnatal visit 36m				
Postnatal visit 48m				
Postnatal visit 60m				

* This is a combined table for Group A and B (and C for HeLTI India) re monitoring data quality by using queries (set rules) to detect issues on missing/incomplete cohort data after being entered in REDCap database; (REDCap is designed according to CRF).

Table 6a. Reportable Serious (Severe) Adverse Events *

REPORTABLE SERIOUS (Severe) ADVERSE EVENTS * To be reported to local Ethics Boards and HeLTI DMC (unexpected and related only) **as they arise**, and table to be submitted to HeLTI DMC for **annual review**	**Group A**	**Group B**
Death		
Mother's death		
Child's death		
Stillbirth Neonatal Death		
Persistent/significant disability/incapacity		
Is Life-threatening		
Maternal/Child ICU admission		
Congenital anomaly		

Note: "Group C" column to be added by HeLTI India.

Table 6b. Reportable Adverse Events **

REPORTABLE ADVERSE EVENTS ** Table to be submitted to HeLTI DMC for **annual review**	**Group A**	**Group B**
Child protective services involvement (voluntary or involuntary)		
Maternal/Child hospitalization		
Suicidal behaviour		
Physical or sexual assault		
Homicidal behaviour		

Note: “Group C” column to be added by HeLTI India.

Table 6c. Reportable Pregnancy and Child Events where Plausibility of Relationship to the Intervention Is Low ***

REPORTABLE PREGNANCY AND CHILD EVENTS where plausibility of relationship to the intervention is low and do not require an event form completion *** Table to be submitted to HeLTI DMC for **annual review**	**Group A**	**Group B**
Severe preeclampsia		
Eclampsia		
HELLP		
Gestational diabetes		
Placental abruption		
Preterm birth <28 weeks Preterm birth 28-31 weeks Preterm birth 32-36 weeks		
Baby NICU admission		
Severe Depression		
Severe Anxiety		

Note: “Group C” column to be added by HeLTI India.

Table 7a. Primary Outcome – Child Adiposity (age 5 years)

Group	N (%)	Participants analyzed
A		
B		

Note: To be filled out when applicable.

Table 8a. Secondary Outcomes (Per Phase)

1) Preconception Phase	**Group A**	**Group B**
Number Participants included in the analysis		
a) Maternal mean BMI (paternal if available) b) Maternal mental health outcomes ((depressive symptoms - EPDS score >12; PHQ-9 >10; anxiety symptoms - GAD-7>=15) (paternal if available) c) Pregnancy Rate		
2) Pregnancy Phase (parental and child outcomes at birth)*		
a) Rate of gestational diabetes; b) Rate of gestational hypertension; c) Rate of pre-eclampsia; d) Pregnancy status – live birth, miscarriage, stillbirth, neonatal death e) Maternal mental health outcomes (depressive symptoms - EPDS score >12; PHQ-9 >10; anxiety symptoms - GAD-7>=15)		
3) Infancy Phase (0-2 years)		
a) Mean child birth weight b) Mean child weight for length z score <2; mean child zBMI at 2 years d) Rates of large- and small- weight for gestational age e) Breastfeeding initiation f) Maternal mental health outcomes (depressive symptoms - EPDS score >12; PHQ-9 >10; anxiety symptoms - GAD-7>=15) (paternal if available)		
4) Early Childhood (3-5 years)		
a) Mean Child zBMI: b) Child Developmental Outcome c) Maternal mean BMI (paternal if available) d) Maternal Mental Health Outcomes: (depressive symptoms - EPDS score >12; PHQ-9 >10; anxiety symptoms - GAD-7>=15) (paternal if available)		

* Analysis is based on women who completed the pregnancy phase

Note:
1. Adaptation will be required according to individual or cluster randomization.
2. Maternal BMI is the last measure before pregnancy (pre-pregnancy BMI).
3. Mean proportion by cluster study is used for categorical variables.
4. Mean of means is used for continuous variables.

Table 9a: Adherence and Compliance of Intervention Visits

Visits *	N Expected visits	N Completed visits	N Missed visits	Visits completed within time window	% Visits completed within time window
V1					
V2					
V3					
V4					

Table 9b: Adherence of Biosample Collection

		Preconception	Prenatal (Pregnancy)			Delivery	Postnatal			
		PCV1	PGV1	PGV2	PGV3	DV4	PN6WK	PN3M	PN6M	PN12M
Total number expected										
		N collected (%)	N collected (%)	N collected (%)	N collected (%)	N collected (%)	N collected (%)	N collected (%)	N collected (%)	N collected (%)
Mother	1. Blood									
	2. Urine									
	3. Stool									
	4. Saliva									
	5. Buccal swab									
	6. Vaginal swab									
	7. Breast milk									
	8. Areola swab									
Father	1. Blood									
Child	1. Cord blood									
	2.PAXgene									
	3. Placenta									
	4. Blood heel prick									
	5 Buccal swab									
	6. Stool									

Note: To be filled out by cohort when applicable.

Appendix 6: Illustrative Letter from DMC to Chairs of Trial Executive Committee where Recommendation Is to Continue the Trial According to the Protocol

[*Date*]

To: Chair of the Trial Executive Committee for (*insert Country*)

Dear [*Chair of Trial Executive Committee for (insert Country)*

The Data Monitoring Committee (DMC) for the HeLTI trials met on [meeting date] to review its progress and interim accumulating data. [*List members*] attended the meeting and reviewed the report.

The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol [*specify protocol version number and date*] with no changes.

We shall next review the progress and data [*provide approximate timing*].

Yours sincerely,

[*Name of meeting Chair*]

Chair of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:

1. [*Insert name and role*]
2. [*Insert name and role*]
3. [*Insert name and role*]
4. [*Insert name and role*]
5. [*Insert name and role*]

Cc HeLTI Research Committee and HeLTI Office