Protocol for a randomised trial evaluating a preconception-early childhood telephone-based intervention with tailored e-health resources for women and their partners to optimise growth and development among children in Canada: a Healthy Life Trajectory Initiative (HeLTI Canada)

ABSTRACT

Introduction The ‘Developmental Origins of Health and Disease’ hypothesis suggests that a healthy trajectory of growth and development in pregnancy and early childhood is necessary for optimal health, development and lifetime well-being. The purpose of this paper is to present the protocol for a randomised controlled trial evaluating a preconception-early childhood telephone-based intervention with tailored e-health resources for women and their partners to optimise growth and development among children in Canada: a Healthy Life Trajectory Initiative (HeLTI Canada). The primary objective of HeLTI Canada is to determine whether a 4-phase ‘preconception to early childhood’ life course intervention can reduce the rate of child overweight and obesity. Secondary objectives include improved child: (1) growth trajectories; (2) cardiometabolic risk factors; (3) health behaviours, including nutrition, physical activity, sedentary behaviour and sleep; and (4) development and school readiness at age 5 years.

Method and analysis A randomised controlled multicentre trial will be conducted in two of Canada’s highly populous provinces—Alberta and Ontario—with 786 nulliparous (15%) and 4444 primiparous (85%) women, their partners and, when possible, the first ‘sibling child.’ The intervention is telephone-based collaborative care delivered by experienced public health nurses trained in healthy conversation skills that includes detailed risk assessments, individualised structured management plans, scheduled follow-up calls, and access to a web-based app with individualised, evidence-based resources. An ‘index child’ conceived after randomisation will be followed until age 5 years and assessed for the primary and secondary outcomes. Pregnancy, infancy (age 2 years) and parental outcomes across time will also be assessed.

Ethics and dissemination The study has received approval from Clinical Trials Ontario (CTO 1776). The findings will be published in peer-reviewed journals and disseminated to policymakers at local, national...
and international agencies. Findings will also be shared with study participants and their communities.

**Trial registration number** ISRCTN13308752; Pre-results.

**BACKGROUND**

Non-communicable diseases (NCDs), including cardiovascular disease, type 2 diabetes mellitus and mental illness, are major global contributors to premature death and disability. In Canada, NCDs account for an estimated 89% of all mortality of which cardiovascular disease accounts for 33% of all deaths. Cardiometabolic disease—hypertension, coronary artery disease and diabetes—has risen in prevalence globally in parallel with economic development, urbanisation, an obesogenic lifestyle and obesity. In Canada, 60% of men and 50% of women are overweight or obese, forecasting serious economic, societal and individual health consequences. Today, 27% of children in Canada are overweight or obese with rates steadily increasing. Accelerated growth in infancy and early childhood is a strong risk factor for obesity in older children. A higher body mass index (BMI) in the preschool-aged child is associated with subclinical atherosclerosis in adulthood. Childhood overweight and obesity can also impact child development, with negative effects found related to cognitive function, social achievement and emotional well-being. This is important given that one in five Canadian children has a mental health problem. Intrauterine and early infancy exposures appear to influence a person’s risk of adult-onset chronic diseases—the core idea of the ‘Developmental Origins of Health and Disease’ hypothesis. Suboptimal maternal nutrition in pregnancy can lead to fetal growth restriction, and a sequence of overcompensatory responses that predispose to cardiometabolic disease in adulthood. Low birth weight and in utero exposure to maternal diabetes, hypertension and obesity are each associated with elevated blood pressure, plasma glucose, insulin and lipid concentrations in children at age 5 years. These childhood risk markers at age 5 years and beyond predict cardiometabolic disease in adulthood.

A similar sequence has been described with a well-studied list of exposures in pregnancy or early infancy: (1) maternal obesity; (2) gestational diabetes (associated with fetal hyperinsulinaemia and excess fetal adiposity); (3) maternal smoking; (4) formula feeding in infancy; and (5) fetal/infant exposure to stress or parental depression.

The preconception period represents an important life stage when exposures can damage germline DNA and epigenetically alter gene expression, subsequently impacting offspring outcomes. A narrative review of preconception interventions to prevent obesity and NCD in children found that no study reported directly on obesity and NCD in children, but rather research to date has focused mainly on pregnancy outcomes and birth weight. Existing approaches tend to focus solely on the mother. Increasingly, scientific evidence shows that the preconception health of the future father is also important, representing an unexplored, underdeveloped and understudied opportunity.

A meta-analysis of 38 studies found a consistent relationship between maternal pre-pregnancy weight and child obesity. Maternal pre-pregnancy obesity is also linked to the hypertensive disorders of pregnancy, gestational diabetes, high infant birth weight and shorter breastfeeding duration. A meta-analysis of 23 trials found that preconception interventions can positively modify maternal health behaviours, including calorie restriction with increased physical activity, that when reinforced by a support system and monitoring can be sustained over longer time periods. Importantly, growing evidence suggests that health behaviour interventions, even those producing a modest change, can successfully and efficiently reduce metabolic disease risk in pregnancy. A meta-analysis of 23 studies found maternal exposure to smoking in pregnancy was associated with increased risk of child obesity. Fetal exposure to maternal smoking impacts prematurity, low birth weight, congenital malformations and sudden infant death syndrome, suggesting psychosocial smoking cessation programmes are warranted before conception. Paternal smoking is also associated with childhood cancer, cardiovascular disease and obesity, not only in the child but grandchildren as well possibly through epigenetic mechanisms. Mental illness is common in women and men of reproductive age, of which a substantial proportion go untreated, especially during pregnancy and postpartum. Parental mental illness negatively affects the entire family and increases a child’s risk for poor cognitive, behavioural and emotional developmental trajectories. The recognised association between mental illness and obesity supports evaluation of whether treating the former preconventionally can reduce the latter. Accordingly, we will deliver evidence-based...
preconception interventions targeting both a woman and her partner, that align with current evidence suggesting that parental BMI, diet, lifestyle and mental health might alter pregnancy and child health outcomes.

The Healthy Life Trajectory Initiative (HeLTI) was developed in partnership with research teams from Canada, China, India and South Africa and in collaboration with the WHO to address the increasing burden of NCDs around the world. Four separate randomised controlled trials implemented in Soweto (South Africa), Mysore (India), Shanghai (China), and the provinces of Ontario and Alberta (Canada) have been harmonised. All trials are focused on developing evidence-based interventions that span from preconception across pregnancy and into the postnatal period with the primary goal of reducing child obesity and improving maternal, paternal, and child health and well-being. The protocol described here is for HeLTI Canada, one of the four trials in the HeLTI initiative.

Consistent with the international HeLTI studies, our main objectives are to determine whether the complete four-phase (preconception, pregnancy, infancy and early childhood) intervention, compared with standard care, can among index children at age 5 years: (1) reduce overweight and obese status; (2) reduce zBMI and improve zBMI trajectories; (3) reduce adiposity; (4) improve cardiometabolic risk factors; (5) enhance development and school readiness; and (6) improve health behaviours, including nutrition, physical activity, screen time and sleep. We will also examine the impact of the intervention on parental outcomes across time. We will determine the ‘cumulative-impact’ of the four-phase intervention, including the effect of the preconception phase on parental outcomes at the time of conception; the effect of the preconception-pregnancy phases on pregnancy outcomes; and the effect of the preconception-pregnancy-infancy phases on child outcomes at age 2 years. Our unique study design also provides an opportunity to understand the effect of the infancy+early childhood phases of the intervention on ‘sibling child’ outcomes at age 5 years. The Glass and McAtee study model provides a general overarching conceptual framework modified based on meta-analytic data on child obesity risk factors. Our study will target modifiable risk factors for childhood obesity during the four phases of the intervention.

**METHODS/DESIGN**

**Study design**

A randomised controlled multicentre trial will be conducted in Canada with 5230 women who are planning to be pregnant within the next 3 years. We will recruit up to 786 nulliparous (15%) and at least 4444 primiparous (85%) women, their partners, and, when possible, the first ‘sibling child.’ These women will be randomly allocated in a 1:1 ratio to the four-phase preconception-early childhood intervention or to usual care, using individual, web-based and central randomisation. An ‘index child’ conceived after randomisation (n=3660; 70%) will be followed until age 5 years and assessed for the primary and secondary outcomes. Pregnancy, infancy (at age 2 years) and parental outcomes will also be assessed. In addition, among the 4444 primiparous women planning their second pregnancy, their preceding first child (called the ‘sibling child’), eligible range 3–12 months when the mother is randomised, will also be followed until age 5 years. This concurrent randomised trial will compare those intervention phases specific to infancy and early childhood versus usual care in these ‘sibling’ children. This added component will allow us to estimate the additional effectiveness of the preconception-pregnancy phases of the intervention (which are only received by the index child), beyond that of the infancy+early childhood phases of the intervention (which are also received by the sibling child), while fully preserving randomisation. Couples who do not conceive will complete an exit assessment 3 years postrandomisation.

**Setting**

The trial will be conducted in two of Canada’s highly populous provinces, Alberta (4.4 million) and Ontario (14.6 million), from three main recruitment settings: (1) public health regions; (2) obstetric and postpartum clinics; and (3) primary care practices and community healthcare centres that provide postpartum and well-child care in Alberta and Ontario. The selected public health regions are strategically located in Edmonton and across Ontario, including rural regions to promote participant diversity. In total, recruitment will be from eight public health regions of which seven are in Southern Ontario (Toronto, Durham, York, Peel, Halton, Hamilton and Niagara) and one is in Alberta (Edmonton). In Edmonton and the surrounding area, the Healthy Living, Population, Public and Indigenous Health team in Alberta Health Services will participate. The obstetric clinics that will participate include those at Mount Sinai Hospital, Sunnybrook Hospital and North York General Hospital. The selected primary care practices are all affiliated with TARGet Kids! in the Greater Toronto Area, where healthy children and their parents are enrolled in a prospective cohort with embedded studies at their primary care practices and followed at their well-child visits. We will also recruit participants via postpartum health clinics (Monarch Centre) in Ottawa and social media including Facebook and Google ads.

**Inclusion/exclusion criteria**

The target population consists of non-pregnant women who meet the following entry criteria: (1) nulliparous (no children) or primiparous (one child) between 3 and 12 months postpartum; (2) planning a pregnancy in the next 3 years; and (3) understands spoken and written English. Excluded are women with (1) type 1 diabetes; (2) parity ≥2; and (3) residence significantly outside of the eight identified health regions or Ottawa area. If a woman has
a twin birth, the first child born will be the index child. Single women and those with same-sex partners will be included.

Study design overview
Our intervention will take a ‘cumulative-impact’ approach designed to improve health behaviours (eg, nutrition, physical activity, screen time and sleep) and reduce modifiable risk factors that influence child obesity. The intervention will start prior to conception and continue through to early childhood. It will be evidence-based, professionally facilitated, proactive, individualised, multi-faceted, and sex-specific and gender-specific. It will build on existing research and clinical resources while recognising the growing trend of e-health.77 Local stakeholders, such as public health nurses/family physicians, will participate in providing services and referrals to ensure the intervention is tailored to local circumstances. Our intervention will target not only women, but also their partners and other key individuals in the child’s environment who can influence child health, such as grandparents, if appropriate. Among primiparous women, we will also provide information and support to promote healthy growth and development with the sibling child with the goal of taking a family-approach to care. Our intervention, with its foundation on public health and primary care platforms and e-health technologies, is structured to facilitate scalability across Canada, if effective.

Preconception-early childhood intervention
The intervention will be provided in four phases: (1) preconception, (2) pregnancy, (3) infancy (0–2 years), and (4) early childhood (3–5 years). Each phase has time-sensitive goals based on child obesity risk factor meta-analyses.46 To achieve these goals, two core strategies will be used throughout the four phases: (1) public health nurse collaborative care and (2) an individualised webpage as part of the responsive HeLTI Canada app that will include expert-selected e-health resources. Systematic reviews for each of these intervention strategies have demonstrated their growing effectiveness in improving health behaviours and clinical outcomes.72-76 We will combine these two different strategies, which will allow us to: (1) reach participants, including those in rural/remote locations or those with transportation limitations; (2) provide support that is convenient and accessible 24 hours/day; (3) offer multiple options for peer/professional support; and (4) deliver care at a low cost.77

Public health nurse collaborative care
Women allocated to the intervention group will be assigned an experienced public health nurse (HeLTI nurse) hired and trained by the team to provide telephone-based collaborative care starting within a week of randomisation. The HeLTI nurses are trained in Healthy Conversation Skills, an evidence-based client-centred programme developed by UK researchers at Southampton University, designed to support health behaviour change.78 The activities provided will include the standard criteria for collaborative care: (1) individual assessment; (2) structured management plan; and (3) scheduled follow-up.

Part I: Telephone assessment
At the beginning of each of the four intervention phases, the assigned HeLTI nurse will telephone the woman, complete an assessment based on phase goals and identify potential preconception risks.

Part II: Structured management plan
The HeLTI nurses’ role will be to: (1) educate the woman and her partner (if applicable) about identified preconception risks and management options; (2) assess management barriers and preferences; and (3) coordinate a management plan with appropriate public health, primary care and community services.

Part III: Scheduled follow-up
The HeLTI nurse will telephone participants every 2 weeks to follow-up on management plans and track targeted behaviours. Based on behaviour modification and reduced risk, the participant will move from the ‘active phase’ of the intervention to the ‘continuation phase’. During this phase, participants will receive telephone follow-up every 2 months until completion of the phase. At the beginning of each phase, participants return to the ‘active phase’ of the intervention with telephone calls every 2 weeks. All participants have the option to proactively call their HeLTI nurse as needed. All intervention activities will be documented including email and text exchanges and referrals to health and social services.

Responsive HeLTI app
A responsive web-based HeLTI Canada app will be developed with easy access functionality. Each woman and her partner will be provided with their own secure login to a site that includes personalised web-based educational materials and apps based on the needs identified by their HeLTI nurse. Our expert-recommended e-health resources and apps will be easily accessible on a mobile device, tablet or computer and will enable us to provide innovative and engaging support to participants with diverse health issues. All e-health resources and apps will be reviewed and updated annually.

Usual care–control group
Women allocated to the control group will have access to standard care provided to all women from preconception to early childhood (child age 5), but they will not receive the preconception-early childhood intervention. However, as a retention strategy, they will also have access to their own individualised webpage with secure login to receive injury prevention and child safety e-health resources based on recommendations from experts from York University and the University of British Columbia.79 Focus groups with parents suggested this would be useful information and the content will not be directly related to the trial primary and secondary outcomes.

Dennis C-L, et al. BMJ Open 2021;11:e046311. doi:10.1136/bmjopen-2020-046311

Open access
and hospitalisation data, and Early Development Instrument data for children. In Ontario, this includes linkage to Better Outcomes Registry and Network Ontario,\textsuperscript{35} a clinical registry with detailed obstetrical and neonatal data for all Ontario in-hospital and out-of-hospital births. Relevant to the current study, this clinical registry will be used to collect data on birth outcomes, including infant birth weight and gestational age. In Alberta, we will use the Alberta Perinatal Health Program, which captures information about all births (and pregnancies).

**Biospecimen collection and management**

It is anticipated that future substudies may require additional biospecimens and supplementary external funding. At baseline, biospecimens will be collected, processed and aliquoted by trained technicians at a province-wide professional lab (LifeLabs) using established standard operating procedures aligned with those outlined at the Global Alliance to Prevent Prematurity and Stillbirth repository. Biospecimens will be stored at Lunenfeld-Tanenbaum Research Institute’s established biorepository. The laboratory fully complies with the Canadian laboratory accreditation programme.

**Sample size**

Current estimates in Canada suggest that ~25% of children at age 5 years are overweight or obese, defined as greater than the 85th percentile for age and sex standardised BMI.\textsuperscript{84} A reduction of overweight and obesity rates of 20% is aligned with the goals of the National Framework for Action to Promote Healthy Weights\textsuperscript{85} and provincial recommendations, including the Ontario Ministry of Health. At age 5 years, 1464 children per group (2928 in total) are required to detect a clinically meaningful 20% relative reduction, corresponding to an absolute reduction of 5% with 90% power at a two-sided alpha of 0.05 for the primary randomised comparison of the preconception-lifecourse intervention versus control. Allowing for 20% attrition from conception to age 5 years, 3660 viable conceptions are required. We expect that an average of 70% of women will conceive within 3 years of recruitment and subsequently give birth. This estimate is conservative: The 2013 guidelines on assessing and treating fertility problems of the UK National Institute of Health and Care Excellence estimate the cumulative probability to conceive a viable pregnancy after 2 years (24 cycles) among women without contraception to be 98% for age 19 to 26% to 90% for age 35–39 years\textsuperscript{86} based on data from a contemporaneous cohort of 782 women from Western European centres.\textsuperscript{81} Estimates in a frequently cited article by Heffner\textsuperscript{87} are somewhat lower, but these are 1-year estimates based on historical cohorts of women\textsuperscript{88} and are still compatible with our assumptions, with an estimated probability of conception of 86% in women aged 20 to 24% to 70% in women aged 35–39 years after 3 years (36 cycles). Therefore, 5230 women will need to be recruited.\textsuperscript{81} The sample size for this trial will also yield more than 95% power to detect a minimal

---

**Figure 1** HeLTI Canada study flow diagram. *Biospecimen data (eg, blood and urine) will also be collected at these time-points from a voluntary subsample of participants who live in the Greater Toronto Area. HeLTI, healthy life trajectory initiative.

**Outcomes and frequency of follow-up**

All participants will be asked to complete online questionnaires via REDCap,\textsuperscript{80} a secure, encrypted web-based electronic data capturing system, at baseline and at scheduled intervals during preconception (12, 24 and 36 months postrandomisation or until conception), pregnancy (24–28 weeks’ gestation), infancy (3, 6, 12 and 24 months following delivery) and early childhood (36, 48 and 60 months following delivery) phases of the trial (Figure 1). Specific outcome measures are presented in table 1. Participants who do not complete any follow-up questionnaires within 2 weeks will be telephoned by a trained research assistant blinded to group allocation to provide a reminder and the REDCap questionnaire link will be resent via email. All women and their partners who complete a questionnaire will be provided with a $C15 gift card. Participants will also be asked to provide clinical data (height, weight, arm and waist circumference, and blood pressure)\textsuperscript{46–48, 81, 82} via a scheduled visit to designated community-based clinics or by home visits, if requested by the participant. Biospecimen data (eg, blood) will also be collected from a voluntary subsample of participants (n=1000) who live in the Greater Toronto Area. We will link health card numbers of consenting mothers, partners and children to provincial health administrative data that will allow for long-term follow-up for inpatient and outpatient physician diagnoses and procedures, including emergency department...
### Table 1  HeLTI Canada outcome measures

#### Primary outcome

| Outcome (at age 5 years)        | Outcome measure                  |
|--------------------------------|----------------------------------|
| Child overweight and obesity prevalence | BMI >85th percentile |

#### Secondary outcomes

| Child outcomes (at ages 2 and 5 years) | Outcome measure                  |
|---------------------------------------|----------------------------------|
| Child anthropometry and adiposity     |                                  |
| BMI (age-standardised and sex-standardised) | zBMI |
| BMI growth trajectories               | zBMI growth rates |
| Waist circumference                    | WHO reference ranges |
| Mid-upper arm circumference            | WHO reference ranges |
| Head circumference                     | WHO reference ranges |
| Adiposity                              | Bioelectrical impedance analysis |

#### Child cardiometabolic risk

| Blood pressure                      | Systolic and diastolic blood pressure |
|-------------------------------------|--------------------------------------|
| Biomarkers                          | Total cholesterol; HDL-cholesterol; triglycerides; non-HDL cholesterol; LDL-cholesterol (Friedewald equation); insulin, glucose, hsCRP |
| Insulin sensitivity and beta cell function | HOMA-IS; HOMA B-cell function |
| Cardiometabolic risk score          | CMR score=zWC+zTRG+z-HDL(−1)+z-glucose+z-SBP |

#### Child health behaviours

| Nutrition                           | Breastfeeding behaviours and the Baby Eating Behaviour Questionnaire and Child Eating Behaviour Questionnaire |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Physical activity and screen time   | Questions adapted from the Canadian Health Measures survey and the Canadian 24-hour Movement Guidelines for the Early Years (0–4 years) |
| Child sleep                         | Parent-report questionnaire and the Brief Screening Questionnaire for Infant Sleep Problems |

#### Child development and mental health

| Language development                | Infant Toddler Checklist and the MacArthur Communicative Development Inventories |
|-------------------------------------|---------------------------------------------------------------------------------|
| Behavioural development            | Strengths and Difficulties Questionnaire                                         |
| Socioemotional development         | Ages and Stages Questionnaire Social Emotional scale                             |
| Temperament                         | Early Childhood Behaviour Questionnaire and Children’s Behavioural Questionnaire   |
| Developmental delay                 | Ages and Stages Questionnaire-3 and the Global Scale for Early Development        |
| Executive function                 | Behaviour Rating Inventory of Executive Function                                 |
| School readiness                   | Early Development Instrument                                                     |
| Parental outcomes                  | Outcome measure                                                                |
| Parental anthropometry, adiposity  |                                                                                  |
| Overweight and obesity rates       | BMI ≥25 and ≥30 kg/m², BMI (continuous)                                          |
| Waist circumference                | WHO reference ranges                                                           |
| Blood pressure                     | Systolic and diastolic blood pressure                                           |
| Blood measures                     | Glucose, HbA1c, CBC and CRP                                                      |
| Parental health behaviours         |                                                                                  |
| Nutrition                           | PrimeScreen                                                                     |
| Physical activity and sedentary behaviours | Global Physical Activity Questionnaire and questions adapted from the International Physical Activity Questionnaires |
| Sleep                               | Pittsburgh Sleep Quality Index                                                  |

Continued
clinically important difference in age-standardised and sex-standardised BMI z-score of 0.25 between groups. Our sample size will yield more than 95% power to detect the minimally clinically important difference of 0.25 SD units between groups. The study design will also allow for evaluation of the infancy to early childhood phase of Parental mental health

| Parental mental health                                      | Outcome measure                                           |
|-------------------------------------------------------------|-----------------------------------------------------------|
| Depressive symptoms (pregnancy and up to 1 year postpartum) | Edinburgh Postnatal Depression Scale<sup>96</sup>         |
| Anxiety symptoms                                            | Generalised anxiety disorder<sup>7</sup>                  |
| Life stress                                                 | Perceived Stress Scale<sup>131</sup>                     |
| Loneliness                                                  | Three-item Loneliness Scale<sup>132</sup>                |

Parental relationships

| Relationship satisfaction                                   | Dyadic Adjustment Scale<sup>133</sup>                    |
| Intimate partner violence                                 | Woman Abuse Screening Tool<sup>134</sup>                 |
| Social support                                             | Social Provisions Scale<sup>135</sup>                   |

Parenting behaviours

| Coparenting                                                | Coparenting Relationship Scale<sup>136</sup>            |
| Parenting style                                            | Parenting Scale<sup>97</sup>                            |
| Parenting competence                                       | Parenting Sense of Competence Scale<sup>137</sup>      |
| Parenting stress                                           | Parenting Stress Index Short-Form (PSI-SF)<sup>99</sup>|

Home environment

| Exposure to tobacco smoke, alcohol and substance abuse, and home/work toxins | CAGE-AID questionnaire,<sup>100</sup> the Alcohol Use Disorders Identification Test<sup>101</sup> and environmental toxin questions adapted from the INTERBIO-21<sup>st</sup> study<sup>138</sup> |

Sociodemographic indicators

| Income, education, immigration status, food and housing insecurity, changes in residence, and development of chronic diseases | HeLTI Canada Sociodemographic Questionnaire |

Pregnancy outcomes

| Data will be obtained from either provincial databases (eg, BORN Ontario) or from the Canadian Institutes for Health Information Discharge Abstract Database, all linked using health card numbers. |                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Weight gain                                                                                                                                       | Net weight gained (kg) (continuous)                      |
| Gestational diabetes                                                                                                                               | OGGT; gestational diabetes diagnosis                     |
| Gestational hypertension                                                                                                                           | Gestational hypertension diagnosis; blood pressure      |
| Pre-eclampsia                                                                                                                                      | Pre-eclampsia diagnosis                                   |
| Preterm delivery                                                                                                                                    | Born <37 weeks gestational age                           |
| Weight for gestational age, birth weight                                                                                                           | Small for gestational age <10th percentile; large for gestational age ≥90th percentile |
| Maternal exposure                                                                                                                                  | Maternal exposure to tobacco smoke, prescribed medication use, alcohol and substance use |
| Health service utilisation                                                                                                                         | ICES Linkage (Ontario)                                   |
| Nature of and satisfaction with intervention                                                                                                      | Intervention Activity Log and Intervention Satisfaction Questionnaire |
| Economic evaluation                                                                                                                               | Cost-effectiveness of the preconception lifecourse intervention<sup>139</sup><sup>148</sup> |
| Epigenetics and genetics outcomes                                                                                                                 | Genetic and epigenomic analyses will be planned when additional funding is received |

BMI, body mass index; BORN, Better Outcomes Registry and Network; CAGE-AID, cut-annoyed-guilty-eye questionnaire adapted to include drugs; CBC, complete blood count; CMR, cardiometabolic risk; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; HeLTI, healthy life trajectory initiative; HOMA, homeostatic model assessment; hsCRP, high-sensitivity C-reactive protein; ICES, Institute for Clinical Evaluative Sciences; IS, insulin sensitivity; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; TRG, triglyceride; WC, waist circumference.
the intervention for the sibling child: Assuming that 85% of women will be primiparous and be randomised when their first, sibling child is aged 6 months (eligible range 3–12 months), up to 4444 children will be included in a concurrent, powered second randomised comparison of the life course intervention received during infancy to early childhood phase versus control. This sample size provides more than 95% power for the same outcome and treatment effect as above after accounting for 20% attrition.

Patient and public involvement

Formative work with over 1300 Canadian families was completed to understand preconception needs, prevalence of preconception risk factors, trial recruitment strategies, intervention preferences and key strategies for disseminating trial results.

Planned analyses

Primary and concurrent secondary randomised comparisons will be analysed independently and hypothesis testing will use a two-sided 0.05 significance level for both comparisons. Since outcomes are identical in the two concurrent comparisons, the same methods will be used. Primary outcome and binary secondary outcomes will be compared by means of a $\chi^2$ test and treatment effects will be expressed as absolute risk differences with 95% CI. Continuous secondary outcomes will be compared by an independent $t$-test and treatment effect will be expressed as the mean difference with 95% CI. Additional analyses of pregnancy and parental outcomes will be done using the same approaches. If baseline values are available for continuous parental outcomes, however, we will use analysis of covariance adjusted for baseline values for these outcomes. As secondary outcomes are considered exploratory in nature, we will not adjust for multiple comparisons.

All outcome data will be analysed according to the intention-to-treat principle, analysing all individuals in the group they were originally allocated to. The primary approach for these analyses will be a complete case analysis, including all individuals with available data. Two types of sensitivity analyses will be performed to account for missing outcome data, using multiple imputation and inverse-probability weighting. Results from these sensitivity analyses will be reported along with the primary analyses. For multiple imputation, we will use baseline characteristics of mothers and outcomes of children in the imputation model to create 20 imputed data sets. Standard errors will be calculated using Rubin’s rules, taking the variability in results between the imputed data sets into account. For inverse-probability weighting, we will calculate the probability of having complete outcome data for each individual using logistic regression; observations will then be weighted by the inverse of these probabilities and outcome models will be built to approximate results of a trial with no missing information. To determine the relative effectiveness of the preconception intervention as compared with the infancy intervention, we will do indirect comparisons that fully preserve randomisation. As up to two children per mother can be included in these analyses, we will use mixed maximum-likelihood logistic and linear regression models, which allow for the correlation of children within families. Prespecified subgroup analyses will be performed by sex and by number of children in the family (one versus two) and accompanied by tests for interaction between treatment effect and subgroup.

Data management and oversight

We will work with the international HeLTI research teams to establish a detailed collaborative plan and governance/management structure to ensure that the HeLTI initiative objectives are met. A data monitoring committee (DMC) has been established. The DMC is independent of sponsors and competing interests. The principal investigators (PIs; Dennis and Birken) of the Canadian team will sit on the international HeLTI Research Committee, while Canadian workgroup leads will contribute to the international HeLTI working groups. At the HeLTI Canada office, an experienced research manager will oversee the whole HeLTI Canada study while a trial coordinator will be responsible for the day-to-day trial management. Research assistants will be hired to perform recruitment activities (detailed explanation about the study, consent form and eligibility screening) while others, blinded to group allocation, will complete follow-up data collection activities for non-responders and gift card management; they will also receive extensive training and will be able to collect any REDCap outcome data via telephone if necessary. HeLTI nurses will be hired and extensively trained to deliver and document the intervention. Women and their partners in both groups will have access to usual standard care across all intervention phases. During depression screens, any participant who has a positive response on the Edinburgh Postnatal Depression Scale (EPDS) self-harm ideation item will be further assessed by trained research staff. In addition, for ethical reasons, local public health nurses will be notified of all participants scoring very high (>20) on any EPDS or Patient Health Questionnaire-9 assessment. We will follow a protocol for infant/child harm if we suspect any potential child abuse/neglect. All these safety strategies have been effectively used previously by Dennis (lead PI). Negative intervention effects will be assessed through participant evaluations. All data will be managed through REDCap, which is fully configurable and incorporates validation rules to ensure high quality data. It allows for remote web-based data entry directly from the participating sites. REDCap will be managed by the Applied Health Research Centre at the Li Ka Shing Knowledge Institute, St. Michael’s Hospital (Toronto).

Nearly one in three Canadian children are overweight or obese, and interventions to prevent obesity have been largely unsuccessful. This randomised controlled trial, conducted with pregnancy planning women and their
partners, will evaluate whether an intervention starting in the preconception period and continued to early childhood can reduce child overweight and obesity, and improve developmental trajectories and mental health, compared with usual standard care. The harmonisation of the intervention and outcomes across the four HeLTI studies (Canada, India, China and South Africa) will enable pooled analysis and direct comparisons. If effective, this telephone-based intervention with e-health resources may be scalable to other sites and settings.

Author affiliations
1Lawrence S. Bloomburg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada
2St Michael’s Hospital, Toronto, Ontario, Canada
3Faculty of Health Sciences, University of Ontario Institute of Technology, Oshawa, Ontario, Canada
4Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
5Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada
6Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
7Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada
8Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada
9Saint Justine Hospital, Montreal, Quebec, Canada
10Department of Health & Society (Scarborough Campus), University of Toronto, Toronto, Ontario, Canada
11Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
12Department of Pediatrics, McGill University, Montreal, Quebec, Canada
13McGill University Health Centre, Montreal, Ontario, Canada
14School of Physical and Occupational Therapy, McGill University, Montreal, Quebec, Canada
15Niagara Region Public Health, Thorold, Ontario, Canada
16Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada
17The Hospital for Sick Children, Toronto, Ontario, Canada
18Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada
19Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, British Columbia, Canada
20Department of Medicine, University of Toronto, Toronto, Ontario, Canada
21Department of Animal Science, McGill University, Montreal, Quebec, Canada
22Faculty of Nursing, University of Calgary, Calgary, Alberta, Canada
23Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada
24Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada
25Department of Physiology, University of Toronto, Toronto, Ontario, Canada
26Monarch Maternal and Newborn Health Centre, Ottawa, Ontario, Canada
27Mount Sinai Hospital, Toronto, Ontario, Canada
28Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada
29Eastern Ontario Health Unit, Cornwall, Ontario, Canada
30Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada
31Ingram School of Nursing, McGill University, Montreal, Quebec, Canada
32Department of Obstetrics and Gynecology, Queen’s University, Kingston, Ontario, Canada
33Centre for Addiction and Mental Health, Toronto, Ontario, Canada
34Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
35Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada
36Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada
37Department of Pediatrics, University of Ottawa, Ottawa, Ontario, Canada
38Women’s College Hospital, Toronto, Ontario, Canada
39Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, Ontario, Canada
40The Ottawa Hospital, Ottawa, Ontario, Canada

Acknowledgements
We thank the families who participated in the formative work to assist us in the development of the Healthy Life Trajectory Initiative Canada trial.

Contributors
CLD and CB are co-principal investigators for Healthy Life Trajectory Initiative Canada. CLD, CB and FM wrote the initial protocol draft. JAD, SA, JB, RB, AB, HBe, HBr, EC, CDC, AF, AG, MJ, KJ, PJ, SK, NL, PL, SL, JLM, GGM, DaM, DdM, KM, AMN, DLO, RSP, AP, MTEP, JR, PR, SS, DS, SS, PSG, GNS, RS, PS, DT, KT, MST, SV and MW read and contributed to the final version. All authors provided edits and critiqued the manuscript for intellectual content.

Funding
This work was supported by Canadian Institutes of Health Research (CIHR), grant number HLC-154502.

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not required.

Ethics approval
Approval provided by Clinical Trials Ontario and the University of Alberta.

Provenance and peer review
Not commissioned; peer-reviewed for ethical and funding approval prior to submission.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Cindy-Lee Dennis http://orcid.org/0000-0002-0135-7242
Flavia Marini http://orcid.org/0000-0003-4158-9563
Rhonda Bell http://orcid.org/0000-0002-4298-9641
Magdalena Janus http://orcid.org/0000-0002-9500-6776
Jonathan L Maguire http://orcid.org/0000-0002-4083-8612

REFERENCES
1 Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the global burden of disease study 2015. Lancet 2016;388:1459–544.
2 Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the global burden of disease study 2013. Lancet 2014;384:766–81.

WHO. Noncommunicable diseases (Ncd) country profiles, 2014.
4 Angkurawaranon C, Jiraporncharoen W, Chenthanakij B, et al. Urbanization and non-communicable disease in Southeast Asia: a review of current evidence. Public Health 2014;128:886–95.
5 Di Cesare M, Benthem J, Stevens GA, et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet 2016;387:1377–96.
6 Zhou B, Benthem J, Di Cesare M, et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet 2017;389:37–55.
7 Federation ID. IDF diabetes atlas. 7th edn, 2015. http://www. diabetesatlas.org/resources/2015-atlas.html
8 Bloom DE, Cañiero ET, Jané-Llopis E. The global economic burden of noncommunicable diseases, 2011.
9 Zhou B, Lu Y, Hajifathalian K, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016;387:1513–30.
10 Raj M. Obesity and cardiovascular risk in children and adolescents. Indian J Endocrinol Metab 2012;16:13.
11 Bergmeier H, Skouteris H, Horwood S, et al. Associations between child temperament, maternal feeding practices and child body mass index during the preschool years: a systematic review of the literature. Obes Rev 2014;15:9–18.
12 Tandon P, Thompson S, Moran L, et al. Body mass index mediates the effects of low income on preschool children’s executive control, with implications for behavior and academics. Child Obes 2015;11:569–76.

Dennis C-L, et al. BMJ Open 2021;11:e046311. doi:10.1136/bmjopen-2020-046311

BMJ Open: first published as 10.1136/bmjopen-2020-046311 on 10 February 2021. Downloaded from http://bmjopen.bmj.com/ on September 17, 2023 by guest. Protected by copyright.
3 Sedgh G, Singh S, Hussain R. Intended and unintended pregnancies worldwide in 2012 and recent trends. *Stud Fam Plan* 2014;45:301–14.

4 Jeong S-K, Nam H-S, Son M-H, et al. Interactive effect of obesity indexes on cognition. *Dement Geriatr Cogn Disord* 2005;19:1–6.

5 Datar A, Sturm R, Maganobasco JL. Childhood overweight and academic performance: national study of kindergartners and first-graders. *Obes Res* 2004;12:58–68.

6 Datar A, Sturm R. Childhood overweight and elementary school outcomes. *Int J Obes* 2008;30:1449–60.

7 Bissel S, Fournier M, Pagani L, et al. Predicting academic and cognitive outcomes from weight status trajectories during childhood. *Int J Obes* 2013;37:154–9.

8 Yang S, Tilling K, Martin R, et al. Pre-Natal and post-natal growth trajectories and childhood cognitive ability and mental health. *Int J Epidemiol* 2011;40:1235–26.

9 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.

10 Michels KB. Early life predictors of chronic disease. *J Womens Health* 2003;12:157–61.

11 Barker DJP. The origins of the developmental origins theory. *J Intern Med* 2007;261:412–7.

12 Warner MJ, Ozaanne SE. Mechanisms involved in the developmental programming of adulthood disease. *Biochem J* 2010;427:333–47.

13 Tam WH, Ma RCW, Yang X, et al. Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: a 15-year follow-up study. *Diabetes Care* 2010;33:1382–4.

14 Boney CM, Verma A, Tucker R, et al. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005;115:e290–6.

15 Krishnavee GN, Sivaksha SN, Jones A, et al. Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress in adolescent Indians. *J Clin Endocrinol Metab* 2015;100:986–93.

16 Barker DJ, Osmond C, Goldberg J, et al. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;298:564–7.

17 Barker DJP, Godfrey KM, Gluckman PD, et al. Fetal nutrition and childhood mortality. *Lancet* 1993;341:398–41.

18 Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. 1992. *Int J Epidemiol* 2013;42:1215–22.

19 Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public health implications. *Am J Clin Nutr* 2011;94:1754S–8.

20 Bao W, Threefoot SA, Srivasan SR, et al. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa heart study. *Am J Hypertens* 1995;8:657–65.

21 Joshi SM, Katrj PJ, Kurnaman K, et al. Tracking of cardiovascular risk factors from childhood to young adulthood — the Pune Children’s Study. *Int J Cardiol* 2014;175:176–8.

22 Wells JCK, Pomery E, Walimbe SR, et al. Elevated susceptibility to diabetes in India: an evolutionary perspective. *Front Public Health* 2016;4:145.

23 Herring SJ, Oken E. Obesity and diabetes in mothers and their children: can we stop the intergenerational cycle? *Curr Diab Rep* 2011;11:20–7.

24 Rayfield S, Pluggé E. Systematic review and meta-analysis of the association between maternal smoking in pregnancy and childhood overweight and obesity. *J Epidemiol Community Health* 2017;71:182–93.

25 Vafeiadi M, Roumeliotaki T, Myridakis A, et al. Association of early promoter methylation at birth is associated with child’s later adiposity. *Diabetes* 2011;60:1528–34.

26 Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol* 2003;23:5293–300.

27 Lillycrop KA, Burridge GC. Epigenetic changes in early life and future risk of obesity. *Int J Obes* 2011;35:72–83.

28 Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* 2008;105:17046–9.

29 Jacob CM, Newell-M. L, Hanson M. Narrative review of reviews of prevention interventions to prevent an increased risk of obesity and non-communicable diseases in children. *Obes Rev* 2019;20:5–17.

30 Dunford AR, Sangster JM. Maternal and paternal periconceptional nutrition as an indicator of offspring metabolic syndrome risk in life through epigenetic imprinting: a systematic review. *Diabetes Metab Syndr* 2017;11:565–62.

31 Woo Biaidal JA, Locks LM, Cheng ER, et al. Risk factors for childhood obesity in the first 1,000 days: a systematic review. *Am J Prev Med* 2016;50:761–79.

32 Bodnar LM, Wisner KL, Mosse-Kolko E, et al. Prepregnancy body mass index, gestational weight gain, and the likelihood of major depressive disorder during pregnancy. *J Clin Psychiatry* 2009;70:1290–6.

33 Leeners B, Rath W, Kuse S, et al. Bmi: new aspects of a classical risk factor for hypertensive disorders in pregnancy. *Clin Sci* 2006;111:81–6.

34 Robinson HE, O’Connell CM, Joseph KS, et al. Maternal outcomes in pregnancies complicated by obesity. *Obstet Gynecol* 2005;106:1357–64.

35 Samuels-Kalow ME, Funai EF, Buhimschi I, et al. Prepregnancy body mass index, hypertensive disorders of pregnancy, and long-term maternal mortality. *Am J Obstet Gynecol* 2007;197:490.e1–6.

36 Chu SY, Kim SY, Schmid CH, et al. Maternal obesity and risk of cesarean delivery: a meta-analysis. *Obes Rev* 2007;8:385–94.

37 GC L, Rouse DJ, Dubrow A. The failure of the increasing prevalence of maternal obesity on perinatal morbidity. *Am J Obstet Gynecol* 2001;185:845–9.

38 Li R, Jewell S, Grummer-Strawn L. Maternal obesity and breastfeeding practices. *Am J Clin Nutr* 2003;77:931–6.

39 Hillson JA, Rasmussen KM, Kiplilhe CL. High prepregnant body mass index is associated with poor lactation outcomes among white, rural women independent of psychosocial and demographic correlates. *J Hum Lact* 2004;20:18–29.

40 Dean SV, Lassi ZS, Imam AM, et al. Preconception care: nutritional risks and interventions. *J Reprod Health* 2011;4:1153.

41 Dean SV, Lassi ZS, Imam AM, et al. Preconception care: closing the gap in the continuum of care to accelerate improvements in maternal, newborn and child health. *Reprod Health* 2014;11:51.

42 Lindström J, Louheranta A, Mannelin M, et al. The finnish diabetes prevention study (Dps): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 2003;26:3230–6.

43 Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ* 2012;344:e2088.

44 Saha S, Gertham U-G, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. *Int J Environ Res Public Health* 2010;7:3150–95.

45 Mitchell JJ, Capua A, Clow C, et al. Twenty-Year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. *Am J Hum Genet* 1996;59:793–8. https://pubmed.ncbi.nlm.nih.gov/8808593

46 Lena-Russo D, Badens C, Aubinard M, et al. Outcome of a school screening programme for carriers of haemoglobin disease. *J Med Screen* 2002;9:57–9.

47 Ahmed S, Saleem M, Modeli B, et al. Screening extended families for genetic hemoglobin disorders in Pakistan. *N Engl J Med* 2002;347:1162–8.

48 Karimi M, Jamalian N, Yaromohammadi H, et al. Premarital screening for -thalassaemia in Southern Iran: options for improving the programme. *Int J Lab Hematol* 2007;29:111–8.

49 Bozkurt G. Results from the North Cyprus thalassaemia prevention program. *Hemoglobin* 2007;31:257–64.

50 Tarazi I, Al Najjar E, Lulu N, et al. Obligatory premarital tests for Tay-Sachs and beta-thalassemia. *Curr Diab Rep* 2010;10:108.

51 Pembrey M, Saffery R, Bygren LO, et al. Human transgenerational responses to early-life experience: potential impact on...
121 Gioia GA, Espy KA, Isquith PK. Behavior rating inventory of executive function, preschool version. Definitions 2020.

122 Janus M, Offord DR. Development and psychometric properties of the Early Development Instrument (EDI): A measure of children’s school readiness. Can J Behav Sci 2007;39:1–22.

123 Linabery AM, Nahhas RW, Johnson W, et al. Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels longitudinal study. Pediatr Obes 2013;8:159–69.

124 Rifas-Shiman SL, Willett WC, Lobb R, et al. PrimeScreen, a brief dietary screening tool: reproducibility and comparability with both a longer food frequency questionnaire and biomarkers. Public Health Nutr 2001;4:249–54.

125 Armstrong T, Bull F. Development of the world Health organization global physical activity questionnaire (GPAQ). J Public Health 2006;14:66–70.

126 WHO. Global physical activity questionnaire (GPAQ) analysis guide. Geneva: World Heal Organsation, 2012: 1–22.

127 Hagström M, Oja P, Sjöström M. The International physical activity questionnaire (IPAQ): a study of concurrent and construct validity. Public Health Nutr 2006;9:755–62.

128 Buyse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

129 Kroenke K, Spitzer RL, Williams JB. The PHQ-9; validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.

130 Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7.

131 Chan SF, La Greca AM. Perceived stress scale (PSS). Encycl Behav Med 2013:1:454–5.

132 Hughes ME, Waite LJ, Hawley LC, et al. A short scale for measuring loneliness in large surveys; results from two population-based studies. Res Aging 2004;26:655–72.

133 Spanier GB. Measuring Dyadic adjustment: new scales for assessing the quality of marriage and similar dyads. J Marriage Fam 1976;38:15–28.

134 Brown JB, Lent B, Brett PJ. Development of the woman abuse screening tool for use in family practice. Fam Med 1996;28:422–8.

135 Caron J. [A validation of the Social Provisions Scale: the SPS-10 items]. Sante Ment Que 2013:38:297–318.

136 Feinberg ME. The internal structure and ecological context of coparenting: a framework for research and intervention. Parent Sci Pract 2003;3:95–131.

137 Gibaud-Wattston I, Wandersman LP. Development and utility of the parenting sense of competence scale. American Psychological Association, 1978.

138 Consortium TI-21st. INTERBIO-21st study protocol, 2012.

139 Hoch JS, Briggs AH, Willan AR. Something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ 2002;11:415–30.

140 Ministry of Health and Long Term Care. Schedule of benefits, 2015: 1–4.