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1. INTRODUCTION

1.1 BACKGROUND

According to population-based data, 7-9% of pregnancies are complicated by hypertension [i.e., diastolic blood pressure (dBP) ≥ 90mmHg](1;2). Approximately 1% of pregnancies are complicated by pre-existing hypertension, 5-6% by gestational hypertension without proteinuria (half present preterm), and 2% by pre-eclampsia (usually defined as gestational hypertension with proteinuria)(3). Pre-existing hypertension presents before pregnancy or before 20 weeks gestation, and may be primary or secondary (e.g., to renal disease)(4). Gestational hypertension presents at ≥ 20 weeks (with/without proteinuria)(5). Pre-existing or gestational hypertension may be non-severe or severe, usually defined as a BP of ≥160-170/110mmHg.

For the planned CHIPS Trial, our focus is women with hypertension that presents at <34 weeks, and is non-severe, non-proteinuric, and either pre-existing (1% of all pregnancies) or gestational (2-3% of all pregnancies). At present, it is unclear how best to manage their non-severe, non-proteinuric hypertension. Current practice approaches include both ‘less tight’ control (allowing BP to be higher than normal) and ‘tight’ control (normalising BP). The effects of each approach on perinatal and maternal outcomes needs to be determined. As emphasized by the apparent perinatal advantages of ‘less tight’ control in the CHIPS Pilot Trial, a definitive RCT, such as the proposed CHIPS Trial, now needs to be conducted.

1.2 RISKS TO THE BABY

Babies born to hypertensive pregnant women have an excess of perinatal complications. It is difficult to ascertain the exact risks by hypertension type due to methodological problems with published studies: most data come from tertiary care centres; definitions of outcomes vary; factors (including antihypertensive therapy) that may confound the BP/fetal growth relationship are not accounted for; studies were undertaken during periods when perinatal care was less advanced; and clinicians have made little progress since 1996 when this was so coherently summarised(6). These concerns notwithstanding, the reported perinatal mortality rate for pregnancies complicated by pre-existing hypertension has been as high as 4% (40/1000)(7-10). For women with either pre-existing or gestational hypertension, the risk of perinatal death or serious morbidity is 16% and ‘high level’ neonatal care as high as 36%/11;12. In 2006, babies of hypertensive mothers represented 14% of neonatal intensive care unit (NICU) admissions in Canada, and 50% had lengths of stay of 11-59 weeks(13).

There are two primary pathways through which babies of hypertensive mothers become sick enough to require ‘high level’ neonatal care: poorer fetal growth and/or perinatal asphyxia. Among women with pre-existing or non-proteinuric gestational hypertension, the risk of a small for gestational age (SGA) infant (<10th centile) is approximately 15%(14-22). Approximately 20% of women with pre-existing hypertension and 40% of women with non-proteinuric gestational hypertension who present before 34 weeks will develop superimposed pre-eclampsia(15;17;23-30), with SGA risk up to 40%(31-37). Perinatal asphyxia may be acute (as a result of placental abruption(38)) or chronic (as a result of chronic uteroplacental insufficiency(39)), at preterm and term gestations(40). These SGA or asphyxiated infants are often admitted to ‘high level’ neonatal care because of short-term complications, such as hypothermia, respiratory failure, and feeding problems(41-46). These infants are at higher risk of adverse neurological outcomes and cognitive function in childhood(47-53). The SGA infants are also at increased risk of cardiovascular and endocrine complications in adulthood(54-62), possibly through fetal programming and/or developmental epigenetic programming in utero (Fetal Programming Hypothesis)(63).

1.3 RISKS TO THE MOTHER

Among non-pregnant women, only if hypertension is very severe and uncontrolled are hypertensive end-organ complications a concern in the short term (i.e., over days to weeks); immediate antihypertensive therapy is then warranted. Among non-pregnant women with non-severe hypertension, hypertensive end-organ complications are a concern only over the long term (i.e., decades); a diagnosis of hypertension is made carefully over months and even when that diagnosis is made, a dBP <100mmHg does not necessarily warrant antihypertensive therapy when women are otherwise well (for example, without renal disease)(64). Thus, any treatment of non-severe hypertension in pregnancy would be based on the potential benefits and risks for the baby.

In addition to the hypertension per se, clinicians have additional concerns about pregnant women with non-severe hypertension because these women are at risk of superimposed pre-eclampsia and its associated end-organ complications. Pre-eclampsia occurs in approximately 20% of women with pre-existing hypertension and 40% of women with non-proteinuric gestational hypertension who present before 34 weeks(15;17;26;65-71). Pre-eclampsia is a disorder of placental development, and the most popular theory describes a mismatch between uteroplacental supply and fetal demands(72). As a result, there is placental release of biological factors that cause systemic maternal endothelial cell dysfunction and the end-organ complications of pre-eclampsia,
which include severe hypertension, eclampsia, pulmonary edema, and HELLP syndrome (haemolysis, elevated liver enzyme, and low platelet syndrome). Although there is consensus that sustained severe hypertension (dBP ≥110mmHg) should be treated with antihypertensive therapy, severe maternal hypertension is a poor surrogate for maternal risk. For example, in published RCTs of pregnant women who received ‘tight’ BP control with antihypertensive therapy, brief episodes of severe hypertension occurred in approximately 11%, but serious maternal complications were rare: no stroke, a single maternal death, and an incidence of eclampsia of <1% (73-78). Therefore, alone, severe hypertension is not considered to be an outcome that would guide clinical practice. Excluding severe hypertension, serious maternal complications occurred in 2-4% of women in our CHIPS feasibility study (79) and CHIPS Pilot Trial (26;80;81).

1.4 POTENTIAL RISKS OF ANTIHYPERTENSIVE TREATMENT

At present, control of maternal BP with antihypertensive therapy is widely available to hypertensive pregnant women. However, as the placenta does not autoregulate blood flow, there is a historical concern that lowering BP may decrease placental perfusion, and because of poorer fetal growth and/or metabolic derangements, babies may do more poorly. This is true regardless of the underlying pathophysiology of the maternal hypertension (Section 2.5). At present, the literature is not robust enough to guide decision-making about optimal use of antihypertensives for non-severe hypertension in pregnancy. CHIPS is designed to address this issue.

1.5 PRINCIPAL RESEARCH QUESTION(S)

Primary: For pregnant women with non-severe, non-proteinuric maternal hypertension at 14-33 weeks, will ‘less tight’ control (target dBP of 100mmHg) vs. ‘tight’ control (target dBP of 85mmHg) increase (or decrease) the likelihood of pregnancy loss or ‘high level’ neonatal care for more than 48hr?

Secondary: Will ‘less tight’ vs. ‘tight’ control increase (or decrease) the likelihood of serious maternal complications?

Other: Will ‘less tight’ vs. ‘tight’ control: i) increase (or decrease) the likelihood of serious perinatal complications; ii) increase (or decrease) the likelihood of severe hypertension and pre-eclampsia; iii) increase (or decrease) the likelihood of maternal satisfaction with care; and iv) result in significant changes in dBP or health care costs?

1.6 THE NEED FOR A TRIAL

The overarching hypothesis underlying CHIPS is that ‘less tight’ control may improve uteroplacental perfusion, fetal growth, and through these, fetal/neonatal well-being. We seek to determine whether ‘less tight’ control (target dBP of 100mmHg) vs. ‘tight’ control (target dBP of 85mmHg) of non-severe maternal hypertension will decrease fetal/neonatal risk without increasing maternal risk.

Over the past 8 years, our research agenda has focussed on setting the groundwork for the CHIPS Trial. We are interested in women with non-severe non-proteinuric hypertension at <34 weeks (3-4% of pregnancies) who are at significant risk of maternal and perinatal complications. Based on meta-analyses of RCTs, arguments can be made for and against ‘less tight’ BP control (Section 1.4) (82-85). ‘Less tight’ control (allowing for higher BP levels) may decrease the risk of SGA infants, but may also increase the risk of transient, severe maternal hypertension, antenatal hospitalisation, and proteinuria at delivery. Our meta-analyses of existing trials do not provide sufficient evidence on which to base clinical decisions because of reporting bias and between-trial heterogeneity in outcome. Currently, guidelines are founded mainly on expert opinion (86-88). In our national survey (1999), Canadian obstetricians were divided on the dBP goal for treatment of non-severe hypertension (89).

In April 03, we started the CHIPS Pilot Trial to determine whether a full CHIPS trial would be possible. In the CHIPS Pilot, we sought to determine whether: clinicians could comply with the interventions, their compliance would result in ‘less tight’ and ‘tight’ control of dBP, there would be a dBP difference between groups, and women were satisfied with their care (26;80;81). From Apr ’03 to Dec ’04, the CHIPS Pilot recruited in 17 centres in Canada, Australia, New Zealand and the UK. Subject inclusion criteria were: dBP 90-109 mmHg, pre-existing/ gestational hypertension, live fetus(es), and 20-33 weeks; women with systolic BP (sBP) ≥ 160mmHg, proteinuria, a contraindication, or major fetal anomaly were excluded. A total of 132 women were randomised to ‘less tight’ (N=66) or ‘tight’ control (N=66). Most clinicians (79% in each group) complied with the intervention. Mean dBP was significantly lower for the ‘tight’ control group: -3.5 mmHg, 95% credible interval [-6.4, -0.6]. Women were satisfied with their care in terms of willingness to have the same treatment again in another pregnancy [60 (92.3%) ‘less tight’ vs. 53 (89.8%) ‘tight’ control] or recommend that treatment to a friend [61 (93.9%) ‘less tight’ vs. 58 (95.1%) ‘tight’ control]. Table 1 shows rates of antihypertensive treatment and other outcomes.
The promising results have now confirmed the feasibility and importance of a trial to determine the effects of 'less tight' vs. 'tight' control of non-proteinuric non-severe pregnancy hypertension on fetal/neonatal illness and serious maternal complications. As such, the proposed CHIPS Trial needs to be conducted now so that clinical management is based on solid evidence. Two international trials of anti-oxidants for pre-eclampsia prevention demonstrated harm(90;91), reminding us that clinical management should not be based solely on promising pilot data or expert opinion, but rather, on definitive RCTs(92).

### 1.7 RELEVANT SYSTEMATIC REVIEW(S)

We conducted three relevant systematic reviews of RCTs prior to designing CHIPS(83;84;93;94), and a relevant Cochrane review has recently been updated(95;96). In these reviews, we have included a total of 31 RCTs (3,462 women) that examined the impact of differential BP control (of non-severe pre-existing(97-102) or gestational(75;76;103-125) hypertension) on maternal and perinatal outcomes. All of these cited trials compared antihypertensive treatment with placebo/no therapy. In the ‘treatment’ groups of cited trials, women were randomised to receive antihypertensive treatment to achieve a dBP of <90mmHg; in the CHIPS Trial, this group is referred to as the ‘tight’ control group. In the placebo or ‘no therapy’ arms of the cited trials, women received placebo or ‘no treatment’, with antihypertensive therapy added if their BP rose to 160-170/100-110mmHg; in the CHIPS Trial, this group is the ‘less tight’ control group. That is, the ‘no treatment’ or placebo arms of the cited trials did in fact receive antihypertensive treatment, if necessary, to control BP. We believe that our terms better reflect the fact that all women in the Trial have dBP observed and have clear plans for management of their BP based on the two policies: either ‘tight’ or ‘less tight’ control of dBP.

There was a tendency for ‘less tight’ control (compared with ‘tight’ control) to be associated with fewer SGA infants (<10th centile) (RR 0.89, 95% CI [0.73, 1.08]). The between-trial heterogeneity in outcome was not fully explained by antihypertensive type and was explored by meta-regression analysis. There was a significant and linear correlation between the decrease in mean arterial pressure, and both an increase in incidence of SGA infants (slope 0.13±0.03, r²=0.54, p=0.002, N=15 trials) and decrease in birthweight (slope -17.55±6.67, r²=0.19, p=0.01, N=34 trials)(84;126). (Spontaneously, when BP is lower in pregnancy, outcomes are worse. A dBP <70mmHg in pregnancy is associated with both lower birthweight and higher perinatal mortality(127). Perinatal and neurodevelopmental outcomes are worse, for preterm and term growth-restricted babies, who are born to normotensive mothers, compared with those born to hypertensive mothers(128;129).) ‘Less tight’ control increased the risk of severe hypertension (RR 2.12 [1.77, 2.53]) and proteinuria at delivery (RR 1.20 [1.02, 1.41]), but there was significant between-trial heterogeneity in outcomes. In 31 trials (3,462 women), there was one maternal death [in the ‘tight’ control group(130) and no reported stroke.

To synthesise the results of the reviews: How best to manage non-severe non-proteinuric hypertension in pregnancy is still unclear. “Tight” control reduces the risk of severe maternal hypertension and proteinuria at delivery, but ‘less tight’ control may decrease the risk of SGA infants. However, the reviews do not provide sufficient evidence to determine the relative benefits and risks of antihypertensive therapy for non-severe pregnancy hypertension. In addition, reporting bias and between-trial heterogeneity in outcome lead to further confusion. Canadian obstetricians are divided on this issue but have indicated a willingness to enrol women into CHIPS(89). Our Pilot Trial demonstrated that ‘less tight’ (vs. ‘tight’) control results in higher dBP, that clinicians can comply with the interventions, and that women are satisfied with their care; there was also a tendency for improved perinatal outcomes associated with ‘less tight’ control. Thus, we believe that the CHIPS Trial is feasible and critically needed.

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**Table 1: CHIPS Pilot Trial maternal and perinatal outcomes** [mean±SD or N (%)]

<table>
<thead>
<tr>
<th></th>
<th>‘Less tight’ control (N=66)</th>
<th>‘Tight’ control (N=65*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive use after randomisation</td>
<td>49 (69.7%)</td>
<td>58 (89.2%)</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>38 (57.6%)</td>
<td>26 (40.0%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>16 (24.2%)</td>
<td>20 (30.8%)</td>
</tr>
<tr>
<td>Serious maternal complications</td>
<td>3 (4.6%)</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Preterm birth (g)</td>
<td>24 (36.4%)</td>
<td>26 (40.0%)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>2675 ± 858</td>
<td>2501 ±855</td>
</tr>
<tr>
<td>Neonatal intensive care unit (NICU) admission</td>
<td>15 (22.7%)</td>
<td>23† (35.9%)</td>
</tr>
<tr>
<td>Serious perinatal complications</td>
<td>9 (13.6%)</td>
<td>14 (21.5%)</td>
</tr>
</tbody>
</table>

* One woman opted not to continue with the Trial.
† One baby was admitted to NICU and subsequently died; in the CHIPS Pilot publication, NICU admission was reported for survivors.

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Choice of antihypertensive agent: There is little to guide the choice of agent. A total of 31 other trials compared one oral antihypertensive with another (most commonly beta-blockers vs. methyldopa), but the same dBP goal was applied to women in both treatment groups(131-161). Beta-blockers (and labetalol in particular) may be more effective antihypertensives than is methyldopa (RR 0.75, 95% 0.58, 0.94) (10 trials, 539 women), but no other differences in maternal or perinatal outcomes were demonstrated (19 trials, 1,282 women)(95). No adverse effects of nifedipine(162), atenolol(163) or methyldopa(164) have been demonstrated on paediatric health or neurodevelopment, but data are too limited to guide the choice of antihypertensive agent. Labetalol and methyldopa are the oral agents used most frequently in Canada(89).

1.8 How the results of the trial will be used
The results of the CHIPS Trial will inform both women and clinicians about treatment of non-severe hypertension, nationally and internationally. Pregnant women will have better information on the impact of treatment on perinatal and maternal outcomes, enabling them to make informed choices, particularly about any ‘trade-offs’ in maternal and fetal risk. National (Society of Obstetricians & Gynaecologists of Canada, Canadian Hypertension Society) and international (International Society for the Study of Hypertension in Pregnancy) specialty societies are in need of high quality evidence in order to inform clinical practice guidelines. This research question has been long-debated without a final conclusion; it will remain highly relevant in 6 years’ time when the final results of the CHIPS Trial will be available.

1.9 Risks to the safety of participants involved in the trial
The interventions of ‘less tight’ and ‘tight’ BP control are both used in current clinical practice and endorsed by international guidelines(88;165;166). There will be no additional risks to women participating in CHIPS, over and above those associated with contemporary recommended therapy for non-severe hypertension. It is possible that there may be some risks associated with either ‘less tight’ or ‘tight’ control, but that is what CHIPS is designed to address. Given uncertainty about maternal and fetal risks associated with policies of ‘less tight’ or ‘tight’ BP control in pregnancy, we plan interim analyses to examine safety (Section 2.17).

2. The trial
Our hypothesis is that ‘less tight’ (vs. ‘tight’) control will be both more effective (result in fewer fetal/neonatal losses or sick babies) and less costly (result in use of fewer health care resources).

2.1 Trial design
CHIPS will be an open, multicentre, international, randomised controlled trial with an intention-to-treat analysis. The study is pragmatic: that is, it will be undertaken to reflect real clinical practice rather than the very tightly controlled circumstances of explanatory trials(167-169). The pragmatic approach is important in this trial, where the interventions are policies of ‘less tight’ and ‘tight’ control, and it is not possible to blind clinicians or patients to the dBP goals of each treatment group. In addition, the policies are complex, consisting of a series of components including the possible treatment, changing dosage, and differential monitoring, all of which reflect the way the treatments would be applied in normal clinical practice(170-172). The primary outcome is outcome for the babies, irrespective of the way the policies are administered.

Eligible women will be randomised centrally to either ‘less tight’ control (aiming for dBP of 100 mmHg) or ‘tight’ control (aiming for dBP of 85mmHg) of their hypertension. Randomisation will be stratified, by both centre and type of hypertension, and blocked.

2.2 Trial interventions

2.2.1 Recruitment and randomisation
Each study site co-ordinator will:

i) identify women who are <34 weeks with non-severe non-proteinuric pre-existing or gestational hypertension;

ii) confirm their eligibility (Section 2.5);

iii) liaise with the maternity care provider to obtain his/her support for the trial;

iv) obtain informed consent;

v) collect baseline data; and

vi) randomise women to one of the two trial groups (Figure 1).
2.2.2 ‘LESS TIGHT’ CONTROL GROUP (FIGURE 2)

The dBP treatment goal is 100mmHg.
For safety, if dBP is ≥ 105mmHg, then antihypertensive medication must be started or increased in dose.
For dBP <100mmHg, antihypertensive therapy should be decreased in dose or stopped, as appropriate.

2.2.3 ‘TIGHT’ CONTROL GROUP (FIGURE 3)

The dBP treatment goal is 85mmHg.
For safety, if dBP is ≤ 80mmHg, then antihypertensive medication must be decreased in dose or discontinued.
If dBP is > 85mmHg, then antihypertensive therapy should be started or increased in dose.

2.2.4 BOTH GROUPS

All BP targets are based on measurements made by a health professional, as CHIPS must be large and international, and will be primarily an outpatient trial run through many obstetric and medical offices.

Korotkoff phase V (disappearance of sounds) should be used for diastolic BP. Korotkoff phase IV (muffling) should be used for diastolic BP only if the Korotkoff sounds are audible as the level approaches 0mmHg.

Self-assessment of BP (at home or elsewhere) may be used. Many home BP monitors have not been validated for use in pregnancy or for women with pre-eclampsia, which will develop in one third of participants in CHIPS(26;173). Thus, changes in antihypertensive medication should not be made based on home BP measurements alone. 24hr ambulatory BP monitoring will not be performed as it is impractical and not widely available.

Most clinicians treat non-severe pregnancy hypertension with either labetalol or methyldopa; both are listed among the drugs of first choice in national and international guidelines(88;174;175). When antihypertensive therapy is required to reach the target dBP, clinicians will be asked to use labetalol in women who are not already on antihypertensives. If there are reasons why labetalol would not be a good choice for a particular woman (e.g., severe asthma), then methyldopa(89) should be prescribed, followed in preference by nifedipine XL(88). The recommended starting doses (and daily maximums) of these antihypertensive agents are as follows: labetalol 100-200 mg BID (max 1200mg/d), methyldopa 250-500mg BID (max 2g/d), nifedipine XL 20-30mg OD (max 120mg/d), and as additional therapy, hydralazine 10mg QID (max 200mg/d). Women currently on an antihypertensive at enrolment may switch to labetalol, or if they prefer, continue on their usual medication, but the following must not be used: ACE inhibitors and angiotensin receptor antagonists (which are fetotoxic), direct renin inhibitors, and atenolol (which may impair intrauterine fetal growth)(88;176).

† If sBP ≥ 160 mmHg, increase dose of existing medication, or start antihypertensive medication, to get sBP < 160 mmHg.
A small patient-held (paper) diary, modelled on that used in the CHIPS Pilot, will be provided to centres for local use. The diary will remind each woman and her caregivers about standardised method of BP measurement and minimise contamination (Section 2.4.1).

There is no standard of care for many obstetric interventions and tests of fetal well-being. CHIPS is a pragmatic trial, and the protocol will allow centres to provide their usual form of care. This may involve differential monitoring which will reflect the way the treatments would be applied in normal clinical practice (177). However, data will be collected on potential co-interventions (e.g., bedrest or hospitalisation) and their impact on outcome examined by secondary analyses (Section 2.16).

2.3 ARRANGEMENTS FOR ALLOCATING PARTICIPANTS TO TRIAL GROUPS
Randomisation will be centrally controlled using the telephone computerised randomisation service at the Data Co-ordinating Centre (DCC) [at the Centre for Mother, Infant, and Child Research (CMICR), University of Toronto] that centres can access 24hr/day using a toll-free line. A back up pager system is maintained at all times to ensure availability of trial staff to handle technical difficulties or questions regarding trial entry. If the automated system fails, hand randomisation will be undertaken. Randomisation will be stratified by centre (to prevent any imbalance between groups in aspects of maternal or neonatal care that may differ between centres) and type of hypertension (in the event that treatment effects differ by type of hypertension). It would not be feasible to conduct the Trial solely among women with either pre-existing or gestational hypertension because of the sample sizes required.

2.4 METHODS FOR PROTECTING AGAINST SOURCES OF BIAS
Masking to the next allocated treatment will be achieved by central randomisation and random block sizes.

Outcomes have been defined to be as objective as possible. It is not possible to mask physicians or patients to the interventions allocated or undertaken. However, for our primary outcome of pregnancy loss or ‘high level’ neonatal care for >48hr, ascertainment will not be biased. There will be central adjudication of the secondary maternal outcome by a committee of relevant experts, who are not involved in the care of women or babies in the trial and who are masked to group allocation (Section 3.2).

Measurement of BP will be as accurate as possible in a large and pragmatic trial such as CHIPS. Clinical BP measurements, at pre-specified intervals in pregnancy, will be an ‘other’ outcome and will be abstracted from the diary or clinical records. These clinical measurements will be taken as part of usual care, and are the BP values that clinicians are responding to in order to achieve the target dBP. 24hr ambulatory BP monitoring will not be performed given its unavailability in all centres and the potential effort and minor discomfort involved. As noted above, self-assessment of BP may be used to monitor dBP, but these measurements should be confirmed before changing antihypertensive therapy to achieve the target dBP (Section 2.2.4).

2.4.1 CONTAMINATION
Women in the ‘less tight’ control group may have their BP normalised; valid reasons include the development of indications for antihypertensive therapy among non-pregnant patients (e.g., renal failure). Women in the ‘tight’ control group may receive ‘less tight’ control, although most reasons for this (e.g., fetal compromise) constitute indications for imminent delivery. Contamination will be minimised by: i) having each woman carry a small diary that will have the target dBP clearly marked on it, and she will present the diary to her caregiver at all outpatient (and if applicable, inpatient) visits; ii) having special study stickers, with the target dBP clearly marked on them for the antenatal notes; and iii) providing women with routine contact with the study co-ordinator (at 14-20, 21-28, 29-33, 34-40 weeks, and at delivery) by telephone or at clinical visits, according to local site logistics; these contacts will allow the co-ordinator to review ongoing compliance with the intervention, and permit reminders (to women and clinicians) at the local level throughout the trial. If after randomisation, women or clinicians change their minds about the allocated treatment, the reason(s) for this will be documented.

2.4.2 CO-INTERVENTIONS
Clinicians and women will not be masked to allocated group. Women in the ‘less tight’ control group may have more antenatal maternal surveillance. Women in the ‘tight’ control group may have more fetal surveillance if fetal growth or monitoring are abnormal. Given that there is no standard of care for many obstetric interventions and tests of fetal well-being, the protocol will allow centres to provide their usual ‘real-world’ care (178). However, a balance between groups in centre-related practices should be achieved by stratification of randomisation by centre. Data will be collected on potential co-interventions such as: numbers/type of outpatient antenatal visits, use of antepartum home care programmes, hospitalisation and/or bedrest, home BP monitoring, and tests of fetal well-being (e.g., non-stress test).
2.5 INCLUSION/EXCLUSION CRITERIA

The target population consists of women with non-severe, non-proteinuric pre-existing or gestational hypertension who are at 14-33\textsuperscript{+6} weeks gestation. It is a historical view that pre-existing and gestational hypertension are completely different entities. Increasingly, there is recognition of a shared underlying pathophysiology (e.g., genetics, metabolic syndrome), and, despite differences in maternal age and environment, there is a convergence of clinical hypertension and cardiovascular events over time(179-181). Women who are (or have been) on antihypertensive medication may be included in the study as long as they meet eligibility criteria, although their antihypertensive medication may be decreased in dose or stopped if they are randomised to ‘less tight’ control of dBP.

2.5.1 INCLUSION CRITERIA

- **Pre-existing or gestational hypertension**: Pre-existing hypertension is dBP ≥ 90mmHg before pregnancy or 20 weeks’ gestation. Gestational hypertension is dBP ≥ 90mmHg that develops after 20 weeks(182).

- **dBP of 90-105mmHg if NOT TAKING antihypertensive therapy, or dBP of 85-105mmHg if TAKING antihypertensive therapy**: Eligibility will be based on BP measurements taken by a health care professional (see Section 2.2.4). dBP must be in the eligible range twice, at least four hours apart, or on two consecutive outpatient visits, with the second measurement being within one week of randomisation. The conventional definition of hypertension (dBP of ≥ 90mmHg) will be used for women not taking an antihypertensive. For women taking an antihypertensive(s), a dBP ≥ 85mmHg will be accepted as indicating hypertension. These women are likely to be hypertensive in the conventional sense when off medication. If women on antihypertensive therapy are randomised to ‘less tight’ control, medication will be decreased/stopped if dBP is < 100mmHg.

- **Live fetus**: Confirmed within one week before randomisation.

- **Gestational age 14-33\textsuperscript{+6} weeks**: As measured by last menstrual period or dating ultrasound(183). Enrolment from 14 weeks (and not earlier) will: minimise enrolment of women who will ultimately miscarry and eliminate theoretical concerns about drug-induced birth defects, and facilitate recruitment of women with pre-existing hypertension early in pregnancy when plans are made for BP management throughout pregnancy. Most importantly, from a neonatal perspective, if one dBP goal is better for the fetus than the other, then this is most likely to be seen with a longer duration of treatment in pregnancy.

2.5.2 EXCLUSION CRITERIA

- **Severe systolic hypertension**: defined as a sBP ≥160mmHg at randomisation(64;184).

- **Proteinuria**: defined as ≥ 0.3g/d by 24hr urine collection, or if a 24hr urine collection is not available, by a urinary protein:creatinine ratio of ≥ 30 mg/mmol or urinary dipstick of ≥ 2+(185).

- **Use of an ACE inhibitor at ≥14\textsuperscript{+6} weeks’ gestation**.

- **Contraindication to either arm of the trial or to pregnancy prolongation**: Contraindications to ‘less tight’ control include renal disease. Contraindications to ‘tight’ control include acute stroke. Contraindications do NOT include fetal compromise (e.g., intrauterine growth restriction, or oligohydramnios), as these fetuses may benefit, in particular, from ‘less tight’ BP control. Women for whom delivery is anticipated within one week should not be enrolled.

- **Known multiple gestation**

- **Known lethal or major fetal anomaly**

- **Plan to terminate pregnancy**

- **Prior participation in the main CHIPS Trial**

2.6 DURATION OF TREATMENT PERIOD

The treatment goal (i.e., ‘less tight’ vs. ‘tight’ control) will be applied from the time of randomisation until delivery (maximum, 28 weeks). Postpartum, clinicians will choose their own BP goals.

2.7 FREQUENCY AND DURATION OF FOLLOW-UP

Babies will be followed until 28 days of life (or primary hospital discharge or 36 weeks corrected gestational age), whichever is later. Women will be followed until 6 weeks after birth or pregnancy loss (or until primary hospital discharge if later).

- **Clinic or study visit within 4 weeks after randomisation**: Women will have their dBP measured by their clinician, and their antihypertensive medication (and any changes at that visit) will be recorded. This information will be used to evaluate compliance in CHIPS.
Other antenatal contact with the site co-ordinator: This will occur at pre-specified times (i.e., 14-20, 21-28, 29-33, 34-40 weeks, and at delivery). Contact will be by clinic visits and/or telephone calls, depending on local site logistics. In so doing, the site co-ordinator will maintain contact with women, encourage ongoing compliance, and assess co-interventions (including treatments and monitoring), and disruption of home and work life. Outcome data will be collected from the maternal and baby’s charts, during the woman’s hospital stay for the birth, and the baby’s hospital stay.

Follow-up at 6-12 weeks post-delivery (or loss) and for preterm babies, when the baby is at 36 weeks corrected gestational age: Contact will be by telephone, clinic or home visit. A standardised questionnaire will be used to inquire about satisfaction with care and any major maternal or neonatal morbidity after hospital discharge until 6 weeks postpartum (for the mother) or 28 days of life or 36 weeks corrected gestational age (for the baby).

2.8 PRIMARY AND SECONDARY OUTCOME MEASURES

2.8.1 PRIMARY: PREGNANCY LOSS OR ‘HIGH LEVEL’ NEONATAL CARE FOR > 48HR

Our primary outcome is a measure of ‘sick’ babies: pregnancy loss or ‘high level’ neonatal care for > 48hr. The outcome is clear-cut and adjudication will not be necessary. For the few women enrolled with unknown multiple gestations, the primary outcome will have occurred if one fetus/neonate achieves the outcome, as the unit of analysis will be women (Section 2.16).

Pregnancy loss is defined as miscarriage, ectopic pregnancy, pregnancy termination, stillbirth, or neonatal death (Table 2). Pregnancy loss is included because all fetuses and neonates must be eligible for the primary outcome. We have included miscarriage and pregnancy termination given proposed enrolment from 14 weeks. Pregnancy termination may occur for static fetal growth, but will most likely be for fetal anomalies, which we expect to be equally distributed between groups. Our sample size calculation has accounted for this (Section 2.11).

‘High level’ neonatal care for > 48hr will be recorded up to 28 days of life or until primary hospital discharge (home) (whichever is later). Among our study population, ‘high level’ neonatal care is common, biologically credible, practical, and measurable, with significant cost implications to the health care system(186). In 2006, babies of hypertensive mothers comprised 14% of NICU admissions in Canada(187). ‘High level’ neonatal care captures neonates who are ‘sick’ through either prematurity, growth restriction or asphyxia, and the outcome is potentially responsive to the intervention of ‘less tight’ control if it improves uteroplacental perfusion, as hypothesized. ‘High level’ neonatal care is meaningful to mothers(188;189). ‘High level’ neonatal care is relevant to preterm and term infants, with the majority of admissions among term infants(190). Parental separation whilst babies are in ‘high level’ neonatal care is a major stressor to parents, even when the baby is not seriously ill(191). As such, this would be an outcome that parents would wish to avoid. Avoidance of parental separation is a long-standing concern of neonatologists(192;193). Finally, ‘high level’ neonatal care is costly ($1,180 to $1,702 per day(194)), even in the absence of morbidities without long-term consequences(195).

A duration of admission of > 48hr has been set to avoid including those babies who are admitted to ‘high level’ neonatal care only briefly for observation or septic work-up. Excluding babies admitted for less than one day is the practice of the Canadian Neonatal Network Database(196;197) and in 2006, only 1.4% of babies of hypertensive mothers stayed in NICU for 24-48hr; 46.5% stayed for 2-10 days (with an equal distribution of length of stay during this time period), 50% stayed for 11-59 days, and 5.4% stayed for ≥ 60 days(198).

Although criteria for admission to, and discharge from, ‘high level’ neonatal care will vary between centres(199;200), randomisation will be stratified by centre to achieve a balance of these practices between groups. Indications for ‘high level’ neonatal care will be documented as ‘other outcomes’ (Section 2.8.3). Criteria for centre participation are based on the ability to immediately resuscitate babies and access ongoing, ‘high level’ neonatal care.

2.8.2 SECONDARY: ONE/MORE SERIOUS MATERNAL COMPLICATION(S)

Serious maternal complications, measured up to 6 weeks postpartum (or until primary maternal hospital discharge, if later), are defined as death or one or more life-threatening maternal complications (as defined in Table 3). Central adjudication by uninvolved individuals will be undertaken (Section 3.2).
### Table 3: Definitions of components of the secondary maternal outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Acute neurological event with deficits lasting &gt; 24 hr, not due to a post-ictal state</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Generalised convulsion in the absence of a history of epilepsy</td>
</tr>
<tr>
<td>Blindness</td>
<td>Either retinal or cortical, defined as loss of visual acuity in the presence of intact pupillary response to light</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>Need for a third parenteral antihypertensive agent</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>Use of vasopressors to keep sBP &gt; 90 mmHg or a MAP &gt; 70 mmHg</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>Diagnosed clinically with one/more of oxygen saturation &lt; 95%, diuretic treatment or x-ray confirmation</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Intubation, ventilation (either by ETT or non-invasively), or need for &gt; 50% oxygen for &gt; 1 hr which is not due to Caesarean section</td>
</tr>
<tr>
<td>Myocardial ischemia or MI</td>
<td>By characteristic ECG changes and markers of myocardial necrosis</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>INR &gt; 1.2 in the absence of DIC or treatment with warfarin, OR, in the presence of DIC or treatment with warfarin: either mixed hyperbilirubinaemia &gt; 17 µM or hypoglycaemia &lt; 2.5 mM in the absence of insulin</td>
</tr>
<tr>
<td>Hepatic haematoma or rupture</td>
<td>Presence of a blood collection under the hepatic capsule as confirmed by imaging or at laparotomy</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Serum creatinine &gt; 200 µM</td>
</tr>
<tr>
<td>Transfusion</td>
<td>Of any blood product</td>
</tr>
<tr>
<td>Other</td>
<td>As detailed, with appropriate information from hospital records</td>
</tr>
<tr>
<td>DIC (disseminated intravascular coagulation), ETT (endotracheal tube), INR (international normalised ratio), MAP (mean arterial pressure), MI (myocardial infarction), sBP (systolic BP)</td>
<td></td>
</tr>
</tbody>
</table>

#### 2.8.3 OTHER OUTCOMES

**Other Perinatal (Table 4)**

| 'High level' neonatal care unit length of stay | Hr and >7 days, including indication for admission                                                                                                                                                                                                                                               |
|---                                             | Male/female/uncertain                                                                                                                                                                                                                                                                             |
| Gestational age at delivery (wk)              | Wk, <37 and >34 weeks                                                                                                                                                                                                                                                                           |
| Birthweight (g)                               | <2500, <1250, <3rd and <10th centile for gestational age and sex[201;202]                                                                                                                                                               |
| Apgar score                                   | 5-min <7, 10-min <5 or <7                                                                                                                                                                                                              |
| Oxygen                                        | After initial resuscitation defined as first 10 minutes of life; duration of oxygen                                                                                                                                                     |
| Ventilatory support                           | After initial resuscitation, with/without intubation; duration of ventilation                                                                                                                                                           |
| Surfactant use                                | Yes/no, # doses                                                                                                                                                                                                                      |
| Severe respiratory distress                  | Requiring assisted ventilation for ≥24 hr beginning within the first 72 hr of life                                                                                                                                                      |
| Respiratory distress                          | Assisted ventilation and supplemental oxygen within the 1st 24 hr of life, for ≥24 hr AND either X-ray compatible with RDS or surfactant given within the 1st 24 hr of life                                                                          |
| Syndrome (RDS)                                | For infants born at <32 wk, supplemental oxygen for a chronic pulmonary disorder at a corrected gestational age of 36 wk                                                                                                               |
| Bronchopulmonary dysplasia                    |                                                                                                                                                                                                                                         |
| Central nervous system morbidity              |                                                                                                                                                                                                                                         |
| Intraventricular haemorrhage                  | Either ventricular enlargement with/without a germinal matrix or intraventricular haemorrhage, by cranial imaging/autopsy in the first 2 wk of life OR parenchymal echodensities/lucencies in the white or gray matter on one/more brain imaging studies/autopsy done after 21d of life[203] |
| Cystic periventricular leukomalacia           | Periventricular cystic changes in white matter, excluding sub-ependymal and choroid plexus cysts, by cranial ultrasound, CT, MRI or at autopsy                                                                                                                                                       |
| Retinopathy of prematurity                    | Stage 4 or 5 in one/both eyes [intraretinal ridge with extraretinal fibrovascular proliferation, or retinal detachment, respectively] by worst stage in the most severely affected eye at 4 wk                                                                                                                   |
| Hyphoxic-ischemic encephalopathy              | For infants born at ≥35 wk who have moderate-severe encephalopathy [clinical seizures or ≥3 of: lethargy, decreased spontaneous activity, distal flexion/full extension, focal/general hypotonia, weak/absent suck or incomplete Moro primitive reflexes, and autonomic system abnormalities (constricted/dilated/deviated/unresponsive pupils, bradycardia or variable heart rate, or periodic breathing/apnea)] AND ≥2 of 10min Apgar <5, cord or postnatal ABG pH < 7.0 within 1hr of birth, cord or postnatal ABG base deficit > 16 µEq/L, or need for any ventilation from birth for ≥10min[204] |
| Parenchymal haemorrhage                       | Yes/no                                                                                                                                                                                                                                 |
| Necrotising enterocolitis                     | For perforation of the intestine, pneumatosis intestinalis or air in the portal vein, diagnosed by x-ray, surgery, or autopsy[205]                                                                                                           |
| 'Early-onset' sepsis                          | Within first 48hr of life, confirmed by positive blood or cerebrospinal fluid cultures                                                                                                                                                |
| Length of stay (hr)                           | Hr                                                                                                                                                                                                                                       |
| Post-discharge morbidity                      | If discharged before 28d of life.                                                                                                                                                                                                       |
### Other Maternal (Table 5)

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Each component of secondary outcome</strong></td>
</tr>
<tr>
<td><strong>Pre-labour dBP at specified time points</strong></td>
</tr>
<tr>
<td><strong>Methods for dBP measurement at compliance visit</strong></td>
</tr>
<tr>
<td><strong>Oral antihypertensive therapy before delivery</strong></td>
</tr>
<tr>
<td><strong>Severe hypertension</strong></td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
</tr>
<tr>
<td><strong>Symptoms of pre-eclampsia</strong></td>
</tr>
<tr>
<td><strong>Signs of pre-eclampsia</strong></td>
</tr>
<tr>
<td><strong>Abnormal maternal laboratory testing</strong></td>
</tr>
<tr>
<td><strong>Mode of delivery</strong></td>
</tr>
<tr>
<td><strong>Days in hospital after delivery</strong></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
</tr>
</tbody>
</table>

### Women’s Views

Using a structured postpartum questionnaire modelled on that used in the CHIPS Pilot, satisfaction (i.e., willingness to have the same treatment again in a subsequent pregnancy or recommend the same treatment to a friend).

### Health-care Costs

The planned analysis will take a ministry of health perspective to determine if ‘less tight’ vs. ‘tight’ control of dBP increases or decreases health-care costs, as discussed in Section 2.10.1

#### 2.9 How outcomes will be measured at follow-up

Data for the primary (fetal/neonatal) and secondary (maternal) outcomes will be obtained by reviewing the maternal and infant medical records immediately following the birth (or pregnancy loss), and then again after the mother’s and infant’s(s’) discharge home. Supplemental information, about potential post-discharge maternal or neonatal morbidities in the 6 weeks following birth for the mother, or 28 days of life for the baby (or 36 weeks corrected gestational age), will be obtained by contacting women at 6-12 weeks postpartum and/or from medical records. Contact will be by telephone, home or clinic visit, as appropriate for the centres; a structured questionnaire will be used to collect the necessary information.

At the time of the study contacts, the local site co-ordinator will abstract the post-randomisation clinical dBP measurements from the patient-held diary that will contain dBP measurements from all obstetric care providers. If the diary is lost, dBP measurements will be abstracted from the structured antenatal sheets that are relatively standardised, based on our experience with international RCTs.

#### 2.10 Health services issues

**2.10.1 Economic evaluation**

The economic hypothesis for the study is that a policy of ‘less tight’ control of maternal BP will result in a lower incidence of pregnancy loss or ‘high level’ neonatal care for > 48hr (without an increase in maternal risk), and therefore, lower health care costs (i.e., a win-win situation). A Ministry of Health perspective will be taken(206). Resources used and their unit prices will be determined. Data will be collected on resources consumed following randomisation and up to 28d of age (or primary hospital discharge if later) for the baby, and 6 weeks following delivery (or primary hospital discharge if later) for the mother. Information will come
from the clinical case report forms. Estimates of unit costs for the mother will be obtained directly from 6 participating hospitals in Canada (three teaching and three community hospitals). Costs considered will include: antihypertensive/other medication; professional fees for outpatient visits; admissions to hospital; obstetric care; tests of maternal or fetal well-being; and neonatal care. Local experts will be interviewed to assist with identification of appropriate fees for each service or treatment.

2.10.2 OTHER HEALTH SERVICES RESEARCH ISSUES
Women’s satisfaction with the intervention and Trial participation will be evaluated (see Section 2.8.3).

2.11 SAMPLE SIZE: 514 women/group (1,028 women total)

We estimate that the rate of pregnancy loss or ‘high level’ neonatal care for > 48hr will be 33%.

- We anticipate that 3% of Trial participants will have a miscarriage, ectopic pregnancy, or elective termination. Based on the CHIPS Pilot Trial, 50% of Trial participants will have pre-existing hypertension, and two-thirds of them may be recruited at 14-20 weeks. Among these women, we anticipate rates of 1% for elective termination and 4% for miscarriage and ectopic pregnancy, giving a figure of 2/3 x5% = 3% overall for miscarriage or elective termination (26).

- We anticipate that 0.4% of Trial participants will have a perinatal loss (stillbirth or neonatal death), based on data from trials published since 1992 (105;207;208) (including the CHIPS Pilot(209)) when there was widespread use of antenatal corticosteroids.

- We anticipate that 30% of babies will be admitted to ‘high level’ neonatal care for > 48hr. This is based on: i) a rate of 31.8% [95% CI 26.5, 37.7] for ‘high level’ neonatal care among trials published since 1992 (105;210-212); ii) in the CHIPS Pilot Trial (the only trial for which this information is available), 23 infants were admitted to ‘high level’ neonatal care, and of these babies, 95.8% stayed for more than one day; and iii) in the Canadian Neonatal Network database for 2006, 98.6% of babies of hypertensive mothers stayed for > 48hr (213).

We have based our sample size on a clinically important reduction in pregnancy loss or ‘high level’ neonatal care for > 48hr from 33% to 25%. When surveyed (Aug ’07), 100% (95% CI of 90% to 100%) of potential site investigator respondents endorsed this decrease as one that would change their clinical practice.

The final sample size of 514/group was based on a two-tailed alpha of 0.05, power of 80%, rates of the primary outcome of 33% in the ‘tight’ control group and 25% in the ‘less tight’ control group (after a crossover of 10% of patients to the alternate treatment), and two interim analyses (after 1/3 and 2/3 of patients have been evaluated for the primary outcome). The sample size was inflated by 1% to account for loss to follow-up. The sample size was calculated by chi-square using the EAST software and the Lan DeMets spending function with O’Brien-Fleming type boundaries. Note that the use of logistic regression for the primary outcome (Section 2.16) increases the statistical power of the analysis (214).

This sample size will give us 78% power (alpha of 0.05, two-sided) to find an increase of 5% in adverse maternal outcome in the ‘less tight’ control group. This is based on a risk of serious maternal complications of 7% in the ‘tight’ control group, based on inclusion of additional maternal outcomes from the PIERS (Preeclampsia Integrated Estimate of Risk Study) project.

2.12 RECRUITMENT

The CHIPS Pilot Trial confirmed the feasibility of the CHIPS Trial. In our survey of Canadian obstetricians, almost all respondents indicated willingness to enrol eligible women in a RCT such as CHIPS (89).

We are interested in women with pre-existing (1%) or gestational hypertension with onset at <34 weeks (2-3%) at 14-33 weeks’ gestation, with prevalence figures cited from population-based literature. Guidelines do not mandate that BP must be repeatedly elevated, despite the fact that transient elevations of BP in pregnancy are well-described. However, to be eligible for CHIPS (as in the CHIPS Pilot Trial), a woman must have persistent hypertension (i.e., DBP ≥ 90 mmHg, twice, at least four hours apart, or on two consecutive outpatient visits, with the second measurement being within one week of randomisation; see Section 2.5.1). Of course, persistent hypertension will be less common than transient hypertension. We believe that such selection of truly hypertensive pregnant women is appropriate, given inaccuracies of BP measurement, and uncertainty about the relative benefits and harms of antihypertensive therapy in pregnancy.

There is a tendency to overestimate recruitment rates (215). We have based our estimated recruitment rate on figures from the CHIPS Pilot, although we expect that recruitment rates will be higher in CHIPS given the measures we have taken to decrease observed barriers to recruitment. In the Pilot, eligible and consenting women made up 0.16% of all deliveries. In a centre with 4,000 deliveries per year, 6 women will be enrolled per year. Based on the EECV2 Trial, we anticipate that 25 centres will join annually. Thus, to complete
enrolment in 4 years, 50 centres will be required. Presently, the CMICR has co-ordinated and is co-ordinating similar large, international RCTs. Recruitment strategies will vary depending on site logistics. In general, women will be informed about the study at prenatal visits (with obstetricians, obstetric internists, family physicians or midwives) or at admission to hospital (if delivery is not imminent; women in labour are not eligible).

2.13 COMPLIANCE

In the CHIPS Pilot, clinician compliance was assessed by a masked adjudication committee that reviewed clinician response to dBP measurements, as recorded in the patient-held diary. Clinician compliance with the interventions was good throughout the trial (79% in both groups). Cross-over was 10% for each arm. It was unclear which type of BP control the others received, although most would have been appropriate for either arm of the Trial. The CHIPS Pilot showed that such a compliance assessment is not feasible for a large trial because it was slow, onerous for those involved, and did not permit contemporaneous feedback at a local level.

For CHIPS, compliance will be determined by assessing dBP and antihypertensive dosage within 4 weeks after randomisation. At this early time point, dBP should not reflect disease progression (primarily development of superimposed pre-eclampsia), and so clinician actions and patient compliance should be reflected in measured dBP. Later in the Trial, dBP will also reflect disease progression. BP will be taken by the woman’s clinician in an unmasked fashion, in the standardised fashion, three times, with the average of the second and third measurements taken as the dBP for that visit (216).

Protocol compliance will be promoted by each site co-ordinator, who will review the patient diary (as done centrally for all women in the CHIPS Pilot) at the planned contacts at 14-20, 21-28, 29-33, 34-40 weeks, and at delivery. Compliance will be checked quarterly for the trial overall, and by centre. If poor protocol compliance is noted generally within a centre, we will work with the centre to identify and resolve the reasons for poor compliance.

2.14 LIKELY RATE OF LOSS TO FOLLOW-UP: 1%

In the CHIPS Pilot, in which women were enrolled from 20-33+6 weeks, our loss to follow-up was 0.8% (1/132 women). CMICR has a history of very low rates of loss to follow-up. In the Term Breech Trial, 2,088 women were recruited from 121 centres world-wide, and only five women (0.2%) were lost to follow-up for the primary outcomes. The possibility of drop-out is higher in CHIPS compared with the Term Breech Trial, in that women may be recruited earlier in pregnancy. However, we shall minimise loss to follow-up by having the site study co-ordinator establish a close relationship with the study participants. The co-ordinator will keep in regular contact with the women and their maternity care providers (Section 2.7), and be available to answer any questions about the Trial. This will facilitate ascertainment of neonatal outcomes (up to 28 days of life, primary hospital discharge, or 36 weeks corrected gestational age) and maternal outcomes (up to 6 weeks postpartum or until primary hospital discharge). Therefore, in the main CHIPS Trial, we will recruit from 14-33+6 weeks, and estimate a loss to follow-up rate of 1% for the primary outcome (i.e., 20 women).

2.15 CENTRES INVOLVED: 50 centres for 4 years

Potential sites participated in the CHIPS Pilot Trial, previously expressed interest in CHIPS, and/or are active participants in ongoing international, clinical trials co-ordinated through CMICR. To date, 60 centres have provided letters of support. These centres are located in Canada, Argentina, Australia, Brazil, Chile, France, Israel, Jordan, Malaysia, New Zealand, South Africa, The Netherlands, UK, and USA.

International collaboration (developed, academic developing world) is required for timely completion of the Trial. For approval by the Working Group (Section 3.1), all interested centres must complete a survey about aspects of their maternal and neonatal care necessary to operationalise the protocol and measure the primary (fetal/neonatal) and secondary (maternal) outcomes for all eligible patients. The Trial Team has extensive experience in conduct of multicentre RCTs, including international research ethics board applications, regulations, and indemnification, through co-ordination of trials such as MACS, MAC5S, Early ECV2, and Twin Birth Study.

2.16 ANALYSES

An intention-to-treat approach will be taken: that is, for the purpose of analysis, all women will be included in the group to which they have been randomised. If women are lost to follow-up, they will be included in their randomised group for all outcomes for which we have information. Descriptive statistics will be calculated to check for major dissimilarities between study groups with respect to baseline information.

The unit of analysis will be women. For the few enrolled women who are found to have multiple pregnancies that were unidentified at enrolment, an outcome for the pregnancy will have occurred if any fetus
suffers the outcome. Outcomes among infants in a multiple pregnancy are correlated, and from the patient perspective, taking home a child with a significant physical or developmental impairment is an outcome that affects the family unit, and not just the child involved. The denominator for ‘high level’ neonatal care admission and length of stay, and neonatal morbidities will be live births. The analysis will be adjusted for any imbalance in multiples between groups.

The primary outcome (of pregnancy loss or ‘high level’ neonatal care for > 48hr) will be analysed by logistic regression, adjusted for stratification factors (centre, type of hypertension), multiple pregnancies (that were not known at randomisation), use of antihypertensive therapy at randomisation, previous severe hypertension in this pregnancy, and gestational diabetes. Alpha will be set at 0.046, based on Lan DeMets spending function with O’Brien-Fleming type boundaries. Table 4 displays the proportion of the overall target number of patients included in the analyses at each point, test statistic, and p-value used to assess significance at each analysis.

For all dichotomous outcomes, logistic regression will be used to compare odds between groups, controlling for any difference between groups on a pre-randomisation factor known or suspected to be a risk factor for the primary or one of the secondary outcomes [e.g., type of underlying hypertension, type and duration of pre-randomisation antihypertensive therapy, recruiting centre]. For dichotomous outcomes, the adjusted OR [95% CI], and number needed to treat (NNT) to avoid one adverse outcome, will be calculated to determine the magnitude of the treatment effect. Significant p-values will be <0.01 (two-tailed) for the secondary and <0.001 (two-tailed) for ‘other’ outcomes (given the number of comparisons and to avoid over-interpretation of statistically significant findings). The NNTs will be based on the adjusted risk differences using methods proposed by Thompson, Warn & Turner(217). As secondary analyses for primary and secondary outcomes, for the purposes of hypothesis generation, we will perform a compliance-adjusted analysis, and an analysis adjusted for any between-group differences in co-interventions (Section 2.13).

Clinical mean dBP will be compared between groups by a repeated measures analysis. It is anticipated that women will be enrolled in the Trial and deliver at different time points, such that BP values will not be available for all of the pre-specified intervals (i.e., 14-20, 21-28, 29-33, 34-40 weeks, and at delivery). As for the CHIPS Pilot(218), the analysis will account for any such imbalance in the repeated measurements of BP. A general linear model will be used with a random effect for patient, and fixed effects for treatment group and time point, fitted using Markov chain Monte Carlo methods facilitated by the software WinBUGS using vague prior distributions(219). P <0.01 will indicate statistical significance to avoid over-interpretation of findings.

### 2.17 FREQUENCY OF ANALYSES

Two interim analyses are planned after enrolment of (and complete data collection for) 1/3 (~338) and 2/3 (~677) of the women. P values of <0.0002 and <0.01203, two-tailed, will be used as guidelines by the Data Safety Monitoring Board (DSMB) at CMICR for considering the early termination of the Trial at the first and second interim analyses, respectively (Section 2.16). If a superior strategy is identified at the second interim analysis, the study may be terminated, and women may be switched to the superior strategy.

### 2.18 PLANNED SUBGROUP ANALYSES

Interaction(s) between treatment effects (e.g., SGA infants) and prognostic factors (e.g., previous pre-eclampsia) or antihypertensive drug will be examined. Rates of the primary and secondary outcomes will be examined by type of hypertension, and for high vs. low perinatal mortality settings. These analyses will be low-powered and considered exploratory.

---

**Table 4: Analyses**

<table>
<thead>
<tr>
<th>Analysis Number</th>
<th>% of patients</th>
<th>N women</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Interim, first)</td>
<td>33.3%</td>
<td>338</td>
<td>3.71</td>
<td>0.00021</td>
</tr>
<tr>
<td>2 (Interim, second)</td>
<td>66.7%</td>
<td>677</td>
<td>2.51</td>
<td>0.01203</td>
</tr>
<tr>
<td>3 (Final)</td>
<td>100%</td>
<td>1,015</td>
<td>1.99</td>
<td>0.046</td>
</tr>
</tbody>
</table>
2.19 **Timeline for the Study:** Each year starts in April (Apr/2008 until Mar/2014 = 6 years)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Develop a manual of operations for DCC &amp; participating centres</td>
<td></td>
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<td>Develop &amp; pre-test data forms and distribute to centres</td>
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<td>Organise Trial in participating centres (including REB approval)</td>
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<td>Program randomisation service</td>
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<td>Develop database</td>
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<td>Recruitment in all centres</td>
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<td>Data collection &amp; management for primary outcome</td>
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<td>Data collection &amp; management for follow-up</td>
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<td>Analyses</td>
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DCC (Data Co-ordinating Centre). REB (research ethics board)

3. **Details of the Trial Team**

3.1 **Arrangements for Day-to-Day Management of the Trial**

**Randomisation** will be centrally controlled using the telephone computerised randomisation service (at the DCC at the CMICR, Toronto) that centres can access 24hr/day using a toll-free line. A back up pager system is maintained at all times to ensure availability of trial staff to handle technical difficulties or questions regarding trial entry. If the automated system fails, hand randomisation will be undertaken.

**Clinical trial co-ordination (Vancouver)** will be managed on a day to day basis at the Maternal-Fetal Medicine Division, Department of Obstetrics & Gynaecology, UBC by a small Working Group that will include Magee, the CMICR Research Manager, and the CHIPS research staff (trial co-ordinator and research assistant). This group will meet weekly by telephone link.

**Data management (Toronto)** will be co-ordinated by the CMICR in close collaboration with Magee (by telephone link). Baseline data will be transmitted to the DCC during the randomisation telephone call. Outcome and other descriptive data will be collected on paper forms and originals mailed to the DCC with copies kept locally. Data will be scanned into a ‘TELEForn’ data management system. This approach has proven to be reliable in previous multicentre RCTs, and will enable CHIPS to be conducted in a variety of settings in which pregnancy hypertension is a major problem, but ready internet access is not available. Logic and range checks will verify the accuracy of the data. Data forms with errors or missing data will be returned to the clinical centres for correction and/or completion.

Dr. Laura Magee is the Principal Investigator and will be responsible for distribution of funds, progress and timely completion of the trial, liaison with participating centres, administration of the study, and answering questions about management of pregnancy hypertension. Dr. Elizabeth Asztalos (Director, CMICR) will be responsible for the work of the Data Co-ordinating Centre.

3.2 **The Steering, Adjudication, and Data Safety & Monitoring Committees**

The **Steering Committee** includes all co-investigators, the CMICR Research Manager, a CIHR representative, and the CHIPS research staff. The Committee will be responsible for the conduct of the study and will meet every two to three months.

A **Maternal Adjudication Committee** of hypertension experts, who are masked to group allocation and uninvolved in the care of women in the trial, will review the recorded serious maternal complications, to confirm inclusion in the secondary maternal outcome.

The CMICR has a **Data Safety Monitoring Board** (DSMB) that will be called upon to monitor compliance and cross-over, and review any unexpected adverse events. The DSMB will meet as required, by teleconference, to review the results of the interim analyses and any unexpected adverse events. The DSMB has the right to review any variables that may have an impact on the trial. The trial has an ISRCTN (71416914) and will be conducted according to Good Clinical Practice Guidelines, and be reported in accordance with the CONSORT statement.
Reference List


(84) von Dadelszen P, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: an updated metaregression analysis. JOGC 2002; 24:941-945.


