TBS

Study Protocol
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1. THE NEED FOR A TRIAL

1.1. What is the problem to be addressed?

1.1.1 Incidence of Twin Births

The rate of multiple births in Canada has increased from 1.9% in 1981 to 2.5% in 1997.[1,2] This increase is likely due to an increase in births to older mothers and increased use of fertility treatments and assisted conception.[2,3] Over 97% of all multiple pregnancies are twin pregnancies.[1] Approximately 40% of twins present as cephalic/cephalic, 35% as cephalic/non-cephalic and the remaining 25% of twins present with twin A in a non-cephalic presentation at birth.[4,5]

1.1.2 Risk of Adverse Perinatal Outcome in Twins

Mortality for twins at 32 or more weeks gestation

The risk of death for twins has decreased over time in Canada, but still continues to be high (see table below).[6]

Table 1 *Gestational age-specific risk of stillbirth & infant death among twin births in Canada**

Gestational Age	1985 – 1987		1994 – 1996	
(weeks)	Stillbirth Rate	Infant Mortality Rate	Stillbirth Rate	Infant Mortality Rate
32-33	2.1/1000	30.5/1000	2.4/1000	20.8/1000
34-36	4.3/1000	13.1/1000	2.7/1000	9.9/1000
37-41	7.7/1000	7.5/1000	4.5/1000	4.8/1000

* Rates of stillbirth are expressed as per 1000 fetuses at risk, infant death rates are expressed as per 1000 live births

Mortality and morbidity for twins vs singletons

Twin pregnancies are at a higher risk of perinatal/neonatal mortality than singleton pregnancies.[7-12] Some of this is due to a higher risk of preterm birth.[11] However, even among twin fetuses that are >2500 g at birth, there is a higher risk of death than among singletons of the same birth weight. Kiely reviewed the data on 16,831 multiple births from the New York City Department of Health's computerized vital records for the period 1978-84.[12] The neonatal mortality rate for twins vs singletons at 2501-3000g and ≥ 3001g was 4.3/1000 vs 3.8/1000 (RR: 1.12) and 7.4/1000 vs 2.2/1000 (RR=3.32), respectively. The intrapartum fetal death rate for twins vs singletons at ≥ 2501g was 1.22/1000 vs 0.34/1000, (RR [95%CI]: 3.54 [1.82, 6.88]). Other studies have confirmed this higher risk of fetal and neonatal death in twins vs singletons if the pregnancy is at or near term or above 2500g in birth weight.[7-10] Neonatal seizures, respiratory morbidity, and low Apgar scores at 1 and 5 minutes have also been shown to be higher for twins vs the singleton infant at birth weights >1500g and >3000g. [9]

Some of the higher risk of adverse perinatal outcome in twins vs singletons, may be due to restricted fetal growth which in turn may result in a higher risk of adverse events occurring during pregnancy, during labour and/or during delivery. The higher risk may also be due to trauma and asphyxia associated with the delivery of the second twin. Some of these adverse outcomes may be avoided by an appropriately timed delivery by caesarean section (CS). In a recently completed multicentre randomised controlled trial (RCT) comparing planned CS and planned vaginal birth (VB) for the singleton breech fetus at term, planned CS was found to reduce the risk of perinatal death or serious neonatal morbidity three fold (from 5.0% to 1.6%, P<0.001).[13] Although some of the deaths in the planned VB group in this study were likely due to difficulties associated with the actual delivery, some were associated with problems that occurred during labour. Thus a policy of planned CS may be beneficial for pregnancies that are at risk of intrapartum complications because it reduces the exposure of the pregnancy to labour.

1.1.3 Evidence that a policy of planned CS might be beneficial for twins at or near term

1.1.3.1 Fetal/perinatal perspective

Outcome for second twin vs first twin

In a recent study of 1305 twin pairs delivered between 1988 and 1999 in Nova Scotia in which second born twins were compared to first born twins at ≥ 1500g birth weight, the risk of adverse perinatal

outcome (intrapartum fetal death, neonatal death, moderate-severe respiratory distress syndrome, asphyxia, trauma, and complications of prematurity) was significantly increased (RR [95%CI]: 2.1 [1.4, 3.1]) for second born twins.[14] There is also evidence that the second twin is at greater risk of adverse perinatal outcome, compared to the first twin if delivery is vaginal but the same has not been shown if delivery is by CS. Arnold and colleagues undertook a matched case-control study of preterm twin pairs.[15] The risk of respiratory distress syndrome was increased for the second twin compared to the first if delivery was vaginal (OR [95%CI]: 14.2 [2.5, 81.1]) but not if delivery was by CS (OR [95%CI]: 0.90 [0, 17.8]).

Outcomes for twins delivered by planned VB (actual VB plus emergency CS) vs planned CS

There has been only 1 RCT of planned CS vs planned VB for twins, in which 60 pairs of twins were enrolled.[16] There were no perinatal deaths or cases of serious neonatal morbidity in either group. The sample size was too small to answer the question of the better approach to delivery. A Cochrane review, incorporating this one trial has recommended that a larger RCT be undertaken.[17]

Because of the limited information from RCTs, we undertook a systematic review of studies that compared the policies of planned VB and planned CS for the delivery of twins weighing at least 1500g or reaching at least 32 weeks gestation.[18] Four small studies were eligible for inclusion in the review.[4,16,19,20] A meta-analysis of the data from the 4 studies did not find significant differences between the two approaches to delivery in terms of mortality or neonatal morbidity, although low Apgar score at 5 minutes was reduced with a policy of CS. This finding, however, was confined to the twins in which twin A presented as a breech.

Outcomes for twins delivered vaginally vs by CS

Higher rates of adverse perinatal outcome have been reported for the twin at or near term if delivery is vaginal vs by CS. In the Kiely review, for twins in cephalic presentation weighing more than 3000g at birth, the neonatal mortality rate was 12.3/1000 vs 2.9/1000 (RR: 4.22) if delivery was vaginal vs by CS.[12]

Importance of fetal presentation

If twin A is breech, there is general agreement that the delivery should be by CS, and these pregnancies are therefore not the subject of this research. Most authors acknowledge that the approach to the delivery of cephalic/non-cephalic twins is controversial.[17,21,22] However, for twins presenting cephalic/cephalic, most clinicians continue to recommend planned VB.[17,22] We believe that planned CS may benefit all twins in which twin A is presenting cephalic for a number of reasons. Firstly, up to 20% of cephalic second twins will change presentation spontaneously after twin A is delivered.[23] Secondly, it was for the twin in cephalic presentation that Kiely found better outcomes if delivery was by caesarean vs vaginal.[12] Thirdly, it is the view of practitioners experienced in the management of labour and the delivery of twins, that a substantial number of those presenting cephalic/cephalic will present with serious acute intrapartum problems following the delivery of twin A (e.g. conversion to transverse lie, cord prolapse, prolonged interval to delivery of twin B), which may lead to emergency CS, perinatal death, and neonatal morbidity. Lastly, if there are benefits to avoiding labour, both twins regardless of presentation should benefit. For these reasons, we believe that planned CS may be better than planned VB as the method of delivery for all twins at or near term, in which twin A is cephalic.

1.1.3.2 Maternal perspective

A policy of planned VB is associated with a 30-40% rate of emergency CS.[13,24] Even among those twins in which twin A is delivered vaginally, there is still a 7% risk of the mother needing to deliver twin B by emergency CS.[24] As the risk of maternal death is highest if delivery is by emergency CS, lowest following a VB, and intermediate following an elective CS,[25] it may be safer from the mother's perspective to have an elective CS than take a 30 - 40% chance of needing an emergency CS. Although a VB is associated with the lowest risk of maternal death and immediate complications in the postpartum period, there is increasing concern regarding the growing evidence of an association between vaginal delivery and urinary incontinence, particularly if the vaginal delivery requires forceps or vacuum

extraction.[26-28] Urinary incontinence identified in the postpartum period has also been shown to have long lasting effects, with a high risk of urinary incontinence 5 years later.[29] Faecal incontinence and incontinence of flatus have also been reported to be associated with vaginal delivery, particularly if forceps are used, and if there are lacerations involving the anal sphincter.[30,31]

In the Term Breech Trial, the RCT of planned CS and planned VB for singleton breech presentation at term, there was no significant difference in maternal mortality or immediate serious maternal morbidity between the 2 approaches to delivery (3.9% vs 3.2%, p=0.35).[32] However, at 3 months postpartum, the women in the planned CS group reported a lower incidence of urinary incontinence (4.5% vs 7.3%, p=0.02). Although the incidence of flatal incontinence was not different between groups, if incontinence of flatus was reported, it was significantly less of a problem in the planned CS group (p=0.006).[32]

Thus from a maternal perspective there are reasons to believe that a policy of planned CS may be beneficial compared to a policy of planned VB if the option of planned VB is associated with a high risk of emergency CS.

1.2. What are the principal research questions to be addressed?

1.2.1 Primary Research Question:

For twin pregnancies of $32^{0/7}$-$38^{6/7}$ weeks gestation, where twin A is presenting cephalic, does a policy of planned CS decrease the likelihood of perinatal or neonatal mortality or serious neonatal morbidity, during the first 28 days after birth, compared to a policy of planned VB?

1.2.2 Secondary Research Questions:

a) For twin pregnancies of $32^{0/7}$-$38^{6/7}$ weeks gestation, where twin A is presenting cephalic, does a policy of planned CS compared to a policy of planned VB decrease the risk of death or poor neurodevelopmental outcome of the children at 2 years of age, corrected for gestational age at birth?; b) For twin pregnancies of $32^{0/7}$-$38^{6/7}$ weeks gestation, where twin A is presenting cephalic, does a policy of planned CS compared to a policy of planned VB decrease the risk of problematic urinary or faecal/flatal incontinence for the mother at 2 years postpartum?

1.2.3 Other Research Questions:

For twin pregnancies of $32^{0/7}$-$38^{6/7}$ weeks gestation, where twin A is presenting cephalic, does a policy of planned CS compared to a policy of planned VB decrease or increase maternal death or serious maternal morbidity (occurring up to 4 weeks following the birth)?; maternal satisfaction with method of delivery determined at 3 months postpartum?; maternal quality of life at 3 months and 2 years postpartum?; maternal depression at 3 months and 2 years postpartum?; breast feeding at 3 months postpartum?; problematic urinary or faecal/flatal incontinence for the mother at 3 months postpartum?; and costs?

1.3. Why is the trial needed now?

Some Term Breech Trial collaborators have indicated that practitioners are extrapolating the results of the Term Breech Trial to twin pregnancies.[33] In 2001, Hutton undertook a survey of Canadian practitioners to determine their views toward different delivery options for twins.[34] Most respondents indicated that for twins at 32 or more weeks gestation in which twin A was cephalic, they would usually recommend a planned VB, with the recommendation of planned VB being as high as 100% for the cephalic/cephalic combination at term to as low as 78% for the cephalic/footling breech combination at 32-36 weeks. However, respondents to the survey were not convinced that planned VB was the best approach to delivery, as 64% indicated they would be willing to enrol their patients with twin pregnancies in a well-designed RCT comparing planned VB with planned CS. The interest in a large twin delivery trial was greatest for twins at term (55%) and for twins presenting cephalic/non-cephalic (58%). However, 48% were willing to enrol women with twins at 32-36 weeks gestation, and 42% were willing to enrol twins presenting cephalic/cephalic.

Many policies in obstetrics have been accepted as the standard of care without adequate evidence to support them. Once a policy of clinical management has been accepted and implemented into practice, it is very difficult to undertake research that is designed to determine the effectiveness of the practice.

Although the Term Breech Trial emphasised the relative safety of a policy of planned CS for the mother, the recently updated Cochrane review has found a higher risk of serious maternal morbidity following a policy of planned CS if the fetus is a singleton breech, and the longer term impact of a policy of planned CS for the mother is not known.[35]

The focus among practitioners has moved away from keeping CS rates low and more towards supporting maternal choice for method of delivery.[36] When the Term Breech Trial was conducted, practice had already shifted towards planned CS. Recruitment to this study was therefore confined to a minority of practitioners who had maintained their skills and confidence in vaginal breech delivery. We believe that a large RCT of planned CS for twins, must be conducted soon before practice changes irreversibly to a policy of planned CS for twins. Indeed the evidence from the Canadian survey suggests that practice may have already moved to some extent towards CS for the twins presenting cephalic/breech. We propose, therefore, a large multicentre international RCT to determine the relative safety of planned CS vs planned VB for term and older preterm twins if twin A is presenting cephalic.

1.4. How will the results of this trial be used?

The results of the trial will be used by obstetricians and other health care providers to counsel women with twin pregnancies about the risks and benefits of the different approaches to delivery, so that women can make a more informed choice as to their planned method of delivery. Policy makers and national specialty societies will use the trial results to develop clinical practice guidelines.

1.5. Risks to the safety of participants involved in the trial

Currently, in the absence of RCT evidence, both CS and VB are used in clinical practice for the delivery of twins. The protocol has been designed to minimise risks to women and their infants, regardless of whether they are randomised to planned CS or planned VB. The protocol will be reviewed by the Research Ethics Boards of all collaborating centres and all women will sign a form indicating their free and informed consent to participation, prior to randomisation. Two interim analyses will be conducted: when complete data are received for the first 1000 women enrolled, and again when complete data are received for the first 1800 women enrolled. The results will be reviewed by an independent Data Safety Monitoring Board (DSMB) to ensure that the differences between groups are not larger than expected. If a larger than expected difference is found, the study will be stopped prior to the enrolment of the full sample size.

2. THE PROPOSED TRIAL

2.1. What is the proposed research design?

To eliminate selection bias, a RCT with prognostic stratification for parity and gestational age at randomisation will be used. Eligible and consenting women will be randomised within parity groups (0 and ≥ 1), and within gestational age groups ($32^{0/7}$-$33^{6/7}$ weeks, $34^{0/7}$-$36^{6/7}$ weeks, and $37^{0/7}$-$38^{6/7}$ weeks) to the planned CS group or the planned VB group, using random block sizes. We will not stratify by centre as we anticipate enrolling only a few women in some centres and stratification by centre would predispose to imbalance and pose a threat to allocation masking.

2.2. What are the planned inclusion/exclusion criteria?

2.2.1 Selection criteria for participants

An ultrasound should be performed within 7 days prior to randomisation to confirm that both fetuses are alive, determine the estimated fetal weights, the presentation of both fetuses, to rule out contraindications to labour or vaginal delivery and to confirm that twins are diamniotic if not previously determined. Twins that are growth restricted may be included in the Twin Birth Study as long as there are no contraindications to labour.

Inclusion Criteria:

1. gestational age $32^{0/7}$-$38^{6/7}$ weeks
2. estimated weight of each fetus is 1,500g – 4,000g
3. both twins must be alive at the time of randomisation; a pregnancy which has been reduced from triplets or a higher order multiple to twins may only be enrolled if the fetal demise occurred before 13 weeks
4. twin A is in cephalic presentation

Exclusion Criteria:

1. monoamniotic twins (monochorionic twins are not excluded from the study; however centres should confirm chorionicity by placental pathology for all same sex twins after delivery so that subgroup analyses can be undertaken for monochorionic and dichorionic twins)
2. lethal fetal anomaly of either fetus
3. contraindication to labour or vaginal delivery of either twin (e.g. intrauterine growth restriction or other evidence of fetal compromise of either twin such that labour would be contraindicated; twin B substantially larger than twin A such that vaginal delivery would be contraindicated; fetal congenital anomaly or condition that might cause a mechanical problem at delivery such as hydrocephalus or cystic hygroma; placenta praevia; previous classical or vertical uterine incision or more than one previous lower segment transverse incision. One previous low segment (transverse incision) CS is not considered a contraindication to labour or vaginal delivery and is thus not a contraindication to participation in the Twin Birth Study.)
4. previous participation in the Twin Birth Study

2.2.2 Selection criteria for participating centres

Participating centres must be able to provide the following care for mothers enrolled in the Twin Birth Study: serial ultrasound monitoring to assess fetal growth at least every 4 weeks; twice-weekly non-stress and/or biophysical profile tests if indicated (for example, for fetuses which are discrepant in growth, or are growth restricted or have risk factors other than the twin pregnancy), continuous electronic fetal heart rate monitoring for twin fetuses in labour; a physician with experience in the management of the labour and delivery of twins must be in attendance for women having a VB (an experienced physician is defined as a qualified obstetrician who judges him/herself to be experienced in the vaginal delivery of twin fetuses and whose Head of Department agrees with this judgement); anaesthetic, obstetrical and nursing staff trained in CS should be present in the hospital at the time of a VB and if necessary, they should be able to undertake an emergency CS within 30 minutes.

Participating centres must be able to provide the following care for infants enrolled in the Twin Birth Study: suitable facilities and qualified neonatal staff who are able to resuscitate a depressed baby by giving oxygen [by mask, bag and mask or ventilator], provide ventilation by endotracheal intubation and positive pressure ventilation, give intravenous therapy and blood transfusion and use surfactant. Centres must be able to obtain a neonatal head ultrasound, if necessary, and must be able to provide two-year follow-up of mothers and children.

2.3. What are the planned trial interventions?

2.3.1 Prior to randomisation:

Women with a known or suspected twin pregnancy will be informed about their possible options for delivery. These will include a planned or elective CS, a planned VB with the option to proceed to CS for one or both twins if problems develop during the pregnancy, labour or delivery, or participation in the Twin Birth Study.

2.3.2 Timing of randomisation:

Women with a twin pregnancy at $32^{0/7}$-$38^{6/7}$ weeks gestation, who meet the selection criteria and consent to participate in the trial, will be randomised. Women may be randomised if they present in labour and/or if they have an indication for urgent delivery (e.g. chorioamnionitis, pre-eclampsia, abruptio placenta) and are otherwise eligible and have given consent.

2.3.3 Timing of Delivery:

Several large studies have shown that the risk of perinatal mortality among twins increases beginning at approximately 38 weeks gestational age, compared with after 41 weeks in the singleton.[7,8,37-40] For this reason the protocol requests that twin pregnancies be delivered before $39^{0/7}$ weeks gestation either by CS or by inducing labour. Because there is evidence that the risk of neonatal respiratory problems increases if elective CS is undertaken prior to 38 weeks,[41] the ideal time to schedule an elective CS is probably around 38 weeks gestation. If there is uncertainty about the gestational age, consideration may be given to confirming fetal maturity by checking the amniotic fluid L/S ratio or managing the pregnancy expectantly using serial fetal monitoring (twice-weekly non-stress and/or biophysical profile tests) until one is confident that the fetuses are mature. Regardless of the presence of additional risk factors, all women who are undelivered at $38^{6/7}$ weeks gestation should proceed to delivery.

2.3.4 Planned CS Group:

Women allocated to the planned CS group should be booked for an elective CS at between $37^{5/7}$ and $38^{6/7}$ weeks gestation. Allowing elective delivery as early as $37^{5/7}$ weeks reflects the current uncertainty as to the best time for elective CS and also provides a slightly larger window of time to arrange for the procedure. If labour begins spontaneously or if there is an indication for delivery before that time, an emergency CS should be undertaken. In the instance of rapidly progressing labour, every effort should be made to proceed to CS before the birth of twin A. If twin A delivers vaginally because a CS cannot be organised in time, delivery should proceed immediately to CS for twin B IF logistically possible. This is because twin B is believed to be at higher risk of poor outcome than twin A and the benefits of a policy of planned CS may be particularly true for the delivery of twin B.[14,15] We anticipate that over 90% of women in the planned CS group will deliver both twins by CS. If a woman allocated to the planned CS group decides, after randomisation, to attempt a VB, she should be managed according to the planned VB protocol.

2.3.5 Planned VB Group:

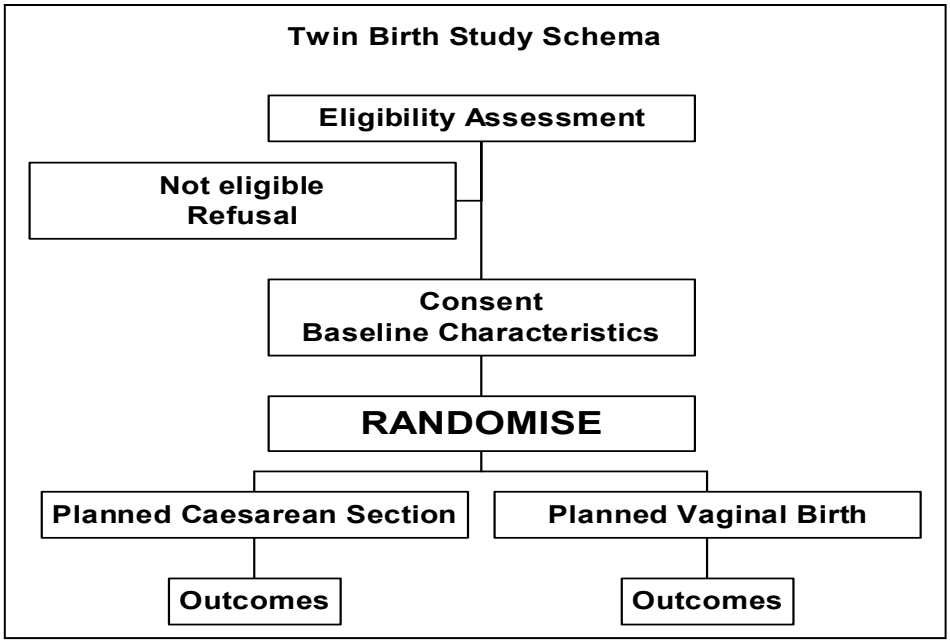
Prior to $37^{5/7}$ weeks gestation, women should await spontaneous labour unless a situation develops necessitating either induction of labour or CS. Women who reach $37^{5/7}$ - $38^{6/7}$ weeks gestation should have labour induced or should undergo CS, if an indication for CS has arisen. Allowing elective delivery as early as $37^{5/7}$ weeks reflects the current uncertainty as to the best time for elective CS or induction of labour and also provides a slightly larger window of time to arrange for the procedure. Reassessment of eligibility for a VB: At the time of labour, each woman should be reassessed to confirm that she is eligible for a VB. Intrapartum management: The intrapartum management for women planning a VB is as follows: *Induction of labour:* Standard methods of induction are recommended such as artificial rupture of membranes, prostaglandins and/or oxytocin, but note that prostaglandins are not generally advised for women with a previous CS. [42] *Oxytocin augmentation:* An intravenous infusion of oxytocin may be used before the delivery of the first twin and/or between twins for hypotonic contractions. *Epidural analgesia:* should be at the discretion of the woman and care provider. *Fetal heart rate monitoring:* Once active labour begins, both fetuses should be monitored continuously, until delivery, using electronic methods. *Assessment of twin B after twin A is delivered:* After the delivery of twin A, consideration should be given to using ultrasound, whenever possible, to confirm the lie and presentation of twin B. *Method of delivery if twin B is cephalic:* Amniotomy should be delayed until the fetal head is engaged in the pelvis to prevent a cord prolapse. If there is no evidence of fetal distress, await spontaneous vaginal delivery; otherwise proceed to operative vaginal delivery using forceps or vacuum or proceed to CS. *Method of delivery if twin B is non-cephalic:* If twin B is non-cephalic, the initial options for delivery are 1. spontaneous or assisted vaginal breech delivery (if breech), 2. total breech extraction with or without internal podalic version, or 3. external cephalic version and vaginal delivery of the fetus as a cephalic. Although there is some evidence that external cephalic version is associated with a higher need for CS for twin B compared to total breech extraction, this in itself does not mean that total breech extraction is preferable in all instances.[20,21,43] The clinician responsible for the delivery should use his/her own judgement as to the best

approach for the delivery of the second twin and document the approach used. We anticipate that over 60% of women in the planned VB group will deliver both twins vaginally.[24] If a woman allocated to the planned VB group decides, after randomisation, to be delivered by CS, she should be managed according to the planned CS protocol.

2.3.6 Both Groups:

a) It should be confirmed that each fetus is alive at the start of labour, before induction of labour and/or before elective CS. If a fetus dies after randomisation and before delivery, the best estimate of the date and time of death should be noted.
b) Pelvic floor muscle training during pregnancy [44-46] and during the first few months postpartum [47, 48] has been shown to reduce the prevalence of postpartum incontinence. All women will therefore be encouraged to undertake pelvic floor muscle exercises and to continue them after delivery.

2.3.7 Schema:



2.4. What are the proposed practical arrangements for allocating participants to the trial groups?

2.4.1 Method of Randomisation:

Randomisation will be centrally controlled using the telephone computerised randomisation service at the University of Toronto Maternal Infant and Reproductive Health Research Unit (MIRU), which centres can access 24 hours per day using a toll-free line. A back up pager system will be maintained at all times to ensure availability of trial staff to handle situations where a technical difficulty is encountered, or where questions arise regarding trial entry. In situations where the automated system fails, hand randomisation will be undertaken.

2.4.2 Timing of randomisation:

Randomisation should ideally be done as close to the time of delivery as possible to minimise contamination. However, women and their caregivers may want time to plan for the delivery and the birth and therefore randomisation may be carried out as early as $32^{0/7}$ weeks gestation if necessary. This may facilitate recruitment into the study. If an eligible woman presents in labour or with an indication for urgent delivery after $32^{0/7}$ weeks but before $39^{0/7}$ weeks gestation and she consents to the trial, she may be randomised.

2.5. What are the proposed methods of protecting against sources of bias?

A centrally controlled computerised randomisation service will be used. It is not possible to mask physicians or patients to the interventions allocated or undertaken. Outcomes have been defined to be as objective as possible. Centres will be asked to provide copies of case notes, autopsy reports, and laboratory reports, to document primary outcomes. An adjudication subcommittee of the Steering Committee will review the neonatal data for all babies in the study, blinded to group of allocation and actual method of delivery, to determine if the criteria for the primary outcome have been met.

2.6. What is the proposed duration of the treatment period?

The treatment period begins at randomisation ($32^{0/7}$-$38^{6/7}$ weeks gestation) and ends with discharge from hospital following delivery.

2.7. What is the proposed frequency and duration of follow-up?

Following discharge from hospital after the birth, women and infants will be followed for 2 years. The occurrence of a neonatal death or an adverse maternal outcome up to 28 days postpartum will be determined by contacting women and/or their physicians by telephone, mail, or by arranging a clinic or home visit. Women will be contacted at 3 months and asked to complete a structured questionnaire to determine satisfaction with the method of delivery, quality of life, depression, breast feeding, and the occurrence of problematic urinary, faecal or flatal incontinence. Women will be contacted at 2 years after delivery and asked to complete a structured questionnaire to determine the neurodevelopmental outcomes of their children, quality of life, depression, and the presence of problematic urinary, faecal, or flatal incontinence. Questionnaires at 3 months and 2 years following delivery will be completed by mail, if possible, otherwise by telephone or during a clinic or home visit.

2.8. What are the proposed outcome measures?

Because the trial interventions are aimed at managing the mother and her pregnancy, the outcomes are analysed for each set (or cluster) of twins (see section 2.11 for details).

2.8.1 Primary Outcome: Perinatal/neonatal mortality and/or serious neonatal morbidity. (excluding lethal congenital anomalies)

In order to justify a policy of planned CS, which may increase the risks of maternal mortality and morbidity, there must be an important benefit for the infants. For each twin, perinatal/neonatal mortality and/or serious neonatal morbidity will be defined as one or more of the following during the first 28 days after birth:

1. Death (either as stillbirth or as a neonatal death 0 to 27 days after birth)
2. Birth trauma defined by any of the following:
    a. Spinal cord injury
    b. Basal skull fracture or depressed skull fracture
    c. Long bone fracture (humerus, radius, ulna, femur, tibia or fibula)
    d. Peripheral nerve injury (brachial plexus palsies, phrenic nerve palsy, facial nerve palsy) present at 72 hours of age (or at discharge from hospital if sooner)
    e. Subdural or intracerebral haemorrhage of any kind (confirmed by ultrasound, computerised tomography [CT] scan, magnetic resonance imaging [MRI], or at autopsy)
3. Apgar score at 5 minutes less than 4
4. Abnormal level of consciousness:
    a. Coma
    b. Stupor or decreased response to pain
5. Neonatal seizures, defined as clonic movements which cannot be stopped by holding the limb, occurring on two or more occasions before 72 hours of age, regardless of cause
6. Need for assisted ventilation $\geq$ 24 hours via endotracheal tube initiated within 72 hours after birth

7. Infection within 72 hrs after birth, defined by either of the following:
    a. Septicemia (positive blood culture)
    b. Meningitis (positive cerebrospinal fluid culture)
8. Necrotising enterocolitis (defined as either perforation of intestine, pneumatosis intestinalis or air in the portal vein) diagnosed by X-ray, surgery, or at autopsy
9. Broncho-pulmonary dysplasia (BPD): need for oxygen at a postnatal gestational age of 36 completed weeks + X-ray compatible with BPD
10. Intraventricular haemorrhage (IVH): Grade III or IV (diagnosed by cranial ultrasound or at autopsy)
11. Cystic periventricular leukomalacia (PVL): Periventricular cystic changes in the white matter excluding subependymal and choroid plexus cysts (diagnosed by cranial ultrasound or at autopsy)

Exclusions for reasons of lethal congenital anomalies will be determined without knowledge of group allocation by an adjudication committee.

2.8.2 Secondary Outcomes:

2.8.2.1 Death or poor neurodevelopmental outcome of the children at 2 years of age (corrected for gestational age at birth)

Neurodevelopmental outcome will be assessed by the Ages and Stages Questionnaire (ASQ).[49] The ASQ is a parent administered questionnaire, which requires a grade 6 reading level to understand and complete, and has been shown to have a low non-response rate. When necessary, the ASQ can be administered by a professional in a clinic setting rather than by the parent alone at home. Reliability testing in 73 parents and 2 examiners has been found to be very good (97%), with a test-retest agreement at 2 week intervals in 68 parents of 99%. When compared with the Bayley Scales of Infant Development, the sensitivity and specificity for the ASQ at 24 months was 84.5% and 79.3% respectively.[49] The ASQ is intended to be used as a screening tool, with those infants scoring in the abnormal range being assessed further by experienced health care professionals. For those children scoring low on the ASQ, a formal clinical neurodevelopmental assessment will be performed by a trained professional to determine if the child is normal or abnormal. An abnormal assessment will be defined as the presence of cerebral palsy or a motor or mental developmental delay of more than 3 months. Children with Down Syndrome, Fragile X, or other chromosomal disorders known to contribute to developmental delay (determined by an adjudication committee masked to allocation group) will be excluded. We have used the ASQ successfully in the international multicentre Term Breech Trial and found it to be easy to administer.

2.8.2.2 Problematic urinary or faecal/flatal incontinence of the mothers at 2 years postpartum.

The occurrence of problematic urinary, faecal/flatal incontinence at 2 years following the birth will be determined by structured questionnaire. Mothers will be asked if they have lost or leaked urine when they coughed, laughed or sneezed, etc. (urinary incontinence), if they have lost or leaked faeces/stool, fluid, or mucous unexpectedly from the bowels (faecal incontinence) and/or if they have passed gas/wind unexpectedly from the bowels (flatal incontinence), within the previous 7 days, as well as how much of a problem the incontinence has been (no problem at all, a little problem, a big problem) whether it be urine, stool or flatus. The seven day recall period will capture information on women who are experiencing regular problematic incontinence. A response indicating that the incontinence is causing a little or a big problem will indicate the presence of problematic incontinence. These are similar to the questions that were used in the Term Breech Trial.[13,32] Women who report problematic incontinence will be asked to complete additional validated questions about the impact of the incontinence, using the IIQ-7. [50]

2.8.3 Other Outcomes:

2.8.3.1 Maternal death or serious maternal morbidity

This is defined as one or more of the following during pregnancy, labour, birth or within the first 28 days following the birth: death; haemorrhage (documented blood loss of ≥1500cc, blood transfusion required, or need for dilatation/curettage after delivery); laparotomy; genital tract injury (hysterectomy,

vulvar or perineal haematoma requiring evacuation, broad ligament haematoma confirmed by ultrasound, CT or MRI, intraoperative damage to bladder, ureter or bowel requiring repair, fistula involving the genital tract, 3rd or 4th degree perineal tear involving the anal sphincter and/or mucosa); thromboembolism (deep vein thrombosis, thrombophlebitis, or pulmonary embolism) requiring anticoagulant therapy; systemic infection (temperature of 38.5° C or more on 2 occasions at least 24 hours apart not including the first 24 hours, or pneumonia [confirmed by X-ray], or sepsis [confirmed by blood culture]); major medical life threatening illness (eg adult respiratory distress syndrome, amniotic fluid embolism, disseminated intravascular coagulation, bowel obstruction, paralytic ileus [requiring naso-gastric suctioning]); wound infection (requiring prolongation of hospital stay, readmission to hospital or repeated treatment as an outpatient), wound dehiscence or wound breakdown, or other serious maternal complication.

2.8.3.2 Maternal satisfaction with method of delivery:
Determined by the mother's willingness to have the same method of delivery again or recommend it to a friend

2.8.3.3 Maternal quality of life: measured by the SF36 [51,52]

2.8.3.4 Maternal fatigue: measured by the Multidimensional Assessment of Fatigue Scale [53]

2.8.3.5 Maternal depression: measured by the Edinburgh Postnatal Depression Scale [54]
A score of >12 will indicate depression

2.8.3.6 Problematic urinary or faecal/flatal incontinence at 3 months:
Women who report problematic incontinence will be asked to complete additional validated questions about the impact of the incontinence, using the IIQ-7.[50]

2.8.3.7 Breast feeding

2.9. How will outcome measures be measured at follow-up?

Outcomes will be determined by reviewing the hospital medical record following the birth for outcomes occurring prior to the mother's and infants' discharge home. The occurrence of a neonatal death and/or adverse maternal outcome during the first 28 days following the birth after discharge from hospital will be determined by contacting women by telephone, or by home or clinic visit. Satisfaction with the birth experience, breast feeding, problematic urinary/faecal/flatal incontinence and quality of life will be determined by structured questionnaire to be completed by the mother at 3 months (satisfaction, breast feeding, incontinence, quality of life, depression) and 2 years (incontinence, quality of life, depression) following the birth. When children are 2 years of age (corrected for gestational age at birth), the mother or other responsible parent, will be asked to complete an ASQ for each child to assess the neurodevelopment of the children. Questionnaires will be completed ideally by mail; otherwise by telephone or by home or clinic visit. If the ASQ scores in the abnormal range, a formal neurodevelopmental assessment will be arranged.

2.10. Will health services research issues be addressed?

2.10.1 Economic evaluation

An economic evaluation is planned for Canadian centres. The economic hypothesis is that planned CS will be better for the twins, and less costly (as a result of fewer poor infant outcomes). The economic evaluation will, by adding a cost component to the evaluation of the interventions, enable decision and policy makers to judge the relative merits of one intervention over the other. A Ministry of Health perspective will be used.

The economic evaluation will involve determining resources consumed and unit prices for these resources. The estimates of unit prices will be combined with the resource use information for all trial participants. Resources consumed in either intervention in the Twin Birth Study will be collected in the clinical case report forms. The estimation of unit prices in this trial will be obtained from a sample of

Canadian participating centres. For the Twin Birth Study, this sample will consist of six hospitals (three smaller/community hospitals and three larger/teaching hospitals).

The unit price estimation within each hospital will involve two stages. First, estimates of professional fees for outpatient doctor visits, daily hospital visits, anaesthesia, and surgical operations will be obtained directly from each appropriate department/ministry of health (third party payer). Local health care experts will be asked to assist with the identification of the most appropriate fees for each service or course of treatment. Second, as existing per diem hospital rates are inadequate for detailed costing purposes, hospital cost models will be developed for each hospital. These models will be constructed with assistance and cooperation from hospital management and finance departments. The models will be designed to estimate department direct expenses, but will also include a share of hospital overhead expenses. Hospital unit price estimates which exclude hospital overhead costs may underestimate substantially the 'true' cost of hospital services. It is for this reason that considerable effort will be devoted to developing reliable and accurate hospital cost models.

2.10.2 Other health service research issues

The trial will examine women's health status, using SF-36, and satisfaction with method of delivery. In addition, women who report problematic incontinence will be asked to complete a short validated questionnaire about the impact of the incontinence: the IIQ-7 for urinary incontinence.[50]

2.11. What is the proposed sample size and what is the justification for the assumptions underlying the power calculations?

We have estimated that the rate of perinatal or neonatal mortality or serious neonatal morbidity in the planned VB group will be approximately 4% of pregnancies. This estimate is based on the rates of adverse perinatal outcome associated with planned VB, found in the systematic review of studies which compared planned CS and planned VB for twins at ≥ 32 weeks gestation,[18] further review of studies of outcomes of twin births, and is consistent with the rates of perinatal mortality or serious neonatal morbidity among twins in Nova Scotia.[24] To further confirm the rate of the primary outcome in the planned VB group, we reviewed the Nova Scotia data (1988 to 2000) using the trial inclusion criteria in women who delivered twins at ≥ 32 weeks gestation where the first twin presented as cephalic, to estimate the rate of primary outcome. The rate of the composite primary outcome was found to be 27/478 (6%) (95%CI: 4% to 8%) of pregnancies among women who had a vaginal delivery, or who had either an emergency CS or a CS in labour. We have decided to retain our conservative estimate of 4% for the purpose of calculating the sample size to allow for the possibility that the Nova Scotia data is an overestimate of the occurrence of the composite primary outcome in other centres, and we wish to be sure that the trial is of sufficient size to definitively answer the research question.

We wish the sample size to be adequate to find a reduction in risk of perinatal or neonatal mortality or serious neonatal morbidity from 4% to 2% with a policy of planned CS, if such a reduction exists, power = 80%, α error = 0.05 (2- sided). The sample size is thus 1250 pregnancies (or sets of twins) per group or a total N=2500. Since we will be treating each set of twins as a cluster in the analysis of the primary outcome, the power will be somewhat higher than 80% depending on the value of the correlation between members of the same twin pair.[55] The higher the correlation the less power will be increased. For a correlation of 0.9 the power is increased to 82% and for a correlation of 0.5 the power is increased to 91%. We expect the correlation to be high, and therefore we will require 2500 women and accept the slight increase in power. If we reduced the sample size based on a correlation that is too low, the power would be reduced.

The required sample size does not take into account the reduction in treatment effect caused by women changing their mind about method of delivery, between the time of randomisation and time of delivery. To allow for such crossovers, the required sample has been increased by approximately 10%, to a **total sample of 2800** (1400 women in each group). For the purposes of analysis, patients will be kept in their original randomised groups (intention to treat principle).

Based on our experience with the Term Breech Trial, we will assume a 20% loss to follow-up at 2 years. We estimate the rate of abnormal neurodevelopmental outcome in the planned VB group will be 2% (based on preliminary analysis [from September 2002] of the risk of abnormal neurodevelopmental assessment in the planned VB arm of the Term Breech Trial). A sample size of 2200 clusters of twins will provide >80% power for finding a reduction in risk of abnormal neurodevelopmental outcome from 2% to 0.5%, α error = 0.05 (2-sided).

We estimate the rate of problematic urinary/faecal/flatal incontinence at 2 years following delivery in the planned VB group will be 15% (based on preliminary analysis [from September 2002] of the risk of problematic incontinence in the planned VB arm of the Term Breech Trial). A sample size of 2200 women will provide >90% power for finding a reduction in risk of incontinence from 15% to 10%, α error = 0.05 (2-sided).

2.12. What is the planned recruitment rate?

We undertook *a pilot study*[56] to ascertain the willingness of women to join the Twin Birth Study. Sixty-four pregnant women with twins were asked to read a patient information sheet and consent form prepared for the Twin Birth Study and to indicate their willingness to participate. Of the 64 women interviewed, 48% said they would be willing to take part in the Twin Birth Study.

We plan to recruit from Canadian centres as well as centres in other countries that are committed to answering this important question and can comply with all aspects of the study protocol. We estimate that approximately 2% of all pregnancies will be twin pregnancies, and that approximately 25% of these will be approached and eligible for the study. Although recruitment rates will vary from one centre to another, we have estimated that the recruitment rate will be on average 30% of eligible twin pregnancies. This estimate is based on the results of our *pilot study*[56] and our experience in the Term Breech Trial, where 20% of women estimated to be eligible agreed to take part. Thus, on average, we anticipate that 0.15% of all births in a centre will participate (for a centre with 4000 births per year, this would be 6 recruits per year). We plan to enrol 2800 women over 4.5 years. Allowing for gradual increases in enrolment over the first 2 years (400/yr, 650/yr, and then 700/yr thereafter) we estimate that we will need 100-150 centres, depending on their size, referral pattern and ability to recruit. To recruit 700/year, we will need centres with approximately 470,000 births per year.

2.13. Are there likely to be any problems with compliance?

Based on our experience with the Term Breech Trial, we do not anticipate problems with compliance. However, we will check compliance with mode of delivery quarterly for the trial as a whole and by centre. If problems occur, we will work with the centres to resolve them.

2.14. What is the likely rate of loss to follow up?

In the Term Breech Trial, we recruited 2088 women from 121 centres world-wide and only 5 women were lost to follow-up for the primary outcomes. The Twin Birth Study follows a similar protocol to that of the Term Breech Trial and thus we anticipate virtually complete follow-up for the primary outcome. The follow-up to 2 years will be more difficult but based on the ongoing follow-up of the Term Breech Trial, we anticipate a follow-up rate of 80%.

2.15. How many centres will be involved?

We have received confirmation from over 120 centres (representing over 470,000 births per year) that they are willing to join the study. The majority of these centres have contributed successfully to our previous and ongoing trials. Due to the large sample size, international collaboration will be required.

2.16. What is the proposed type and frequency of analyses?

Analyses of outcomes measured on both members of each twin pair will be those appropriate for a stratified cluster randomised trial.[57]

Interim analyses: There will be two interim analyses: the first after complete data have been received on the first 1000 women recruited to the study and the second after complete data have been received on

the first 1800 women recruited. Baseline data, data describing the compliance with the intervention and the primary outcome data will be presented in tabular form, using an intention to treat approach, masked to allocation group, to an independent DSMB. If the difference between groups in the primary outcome is different at $p < 0.002$ (2 sided), the trial will be stopped; otherwise recruitment will continue until the full sample size has been accrued.

Final analysis: An intention to treat approach, which includes all mothers and fetuses as randomised, will be used. Descriptive statistics (means, standard deviations, proportions) will be calculated to check for any major dissimilarities in the study groups with regard to patient demographics and other baseline information. Methods proposed by Donner and Klar[57] will be used to compare the rates of the primary outcome, perinatal/neonatal mortality and/or serious neonatal morbidity between the two study groups controlling for the stratification variables (parity [0, ≥ 1], gestational age at randomisation [$32^{0/7}$-$33^{6/7}$, $34^{0/7}$-$36^{6/7}$, $37^{0/7}$-$38^{6/7}$ weeks]) and other prognostic factors (maternal age [<30, ≥ 30 years], presentation of twin B at randomisation [cephalic, non-cephalic], chorionicity [58] [dichorionic, monochorionic[§]], and the country's national perinatal mortality rate (PMR) (per 1000) as reported by the World Health Organisation [59] [<15, 15-20, >20]). Mixed effects models will be used to determine if treatment effects vary between centres and to test for interactions between prognostic factors and treatment. A similar analysis will be performed for the neurodevelopmental outcome. Logistic regression will be used to compare the rates of problematic incontinence at 2 years between groups, controlling for prognostic factors. The level of statistical significance for the analysis of the primary and secondary outcomes will be $p < 0.05$ (two-sided). Adjusted odds ratios and 95% confidence intervals will be calculated to determine the magnitude of the association between the two study groups and the primary and secondary outcome measures. The number of additional CS needed (number needed to treat) to prevent one adverse outcome will also be calculated.

We will use logistic regression to calculate the adjusted odds ratios and 95% confidence intervals for the comparison of the two study groups with respect to the rates of the following other outcome measures: problematic incontinence at 3 months, satisfaction with the birth experience, depression, and breast feeding. The two study groups will be compared with respect to quality of life (SF-36) using a repeated measures ANOVA. The level of statistical significance for the analysis of the other outcomes will be $p < 0.01$ (two-sided).

2.17. Are there any planned subgroup analyses?

For the Term Breech Trial, we found that subgroup analyses were important and helpful for clinicians who were faced with the need to change their clinical practice from vaginal delivery to CS. We therefore plan several subgroup analyses for the Twin Birth Study. For the primary outcome and for the secondary outcome of abnormal neurodevelopment at 2 years, subgroup analyses will be undertaken by parity, gestational age at randomisation, maternal age, presentation of twin B at randomisation, chorionicity and country's national PMR. For the outcome of problematic incontinence, subgroup analyses will be undertaken by parity, maternal age, country's national PMR and history of incontinence prior to pregnancy. Analyses will involve testing for interactions between the factor and treatment group for the outcome.

2.18. Has any pilot study been carried out using this design?

The Term Breech Trial serves as a pilot for the proposed Twin Birth Study: this study uses similar methods of recruitment, randomisation and data collection, and the outcomes are measured in similar ways. In addition, a pilot study[55] was undertaken to ascertain the willingness of women to join a study such as the Twin Birth Study. Women presenting with twin pregnancies (at 28-37 weeks gestation) at Sunnybrook and Women's College Health Science Centre and Mount Sinai Hospital, Toronto, were asked, after they had read the patient information sheet and consent form, if they would be willing to take

[§] centres should determine or confirm chorionicity by placental pathology for all same sex twins

part in the Twin Birth Study. Results indicate that 48% of those approached would be willing to take part. We have used this information in estimating the likely recruitment rate and number of centres needed for the trial (sections 2.12 and 2.15).

3. TRIAL MANAGEMENT

3.1. What are the arrangements for day-to-day management of the trial?

The trial will be managed on a day to day basis, in MIRU, by a small working group which will include Barrett, Hannah (the MIRU Director), Hewson (MIRU Research Manager) and the Study Staff (Trial Co-ordinator, Data Manager, Research Assistant). This group will meet weekly.

3.2. What will be the role of each applicant?

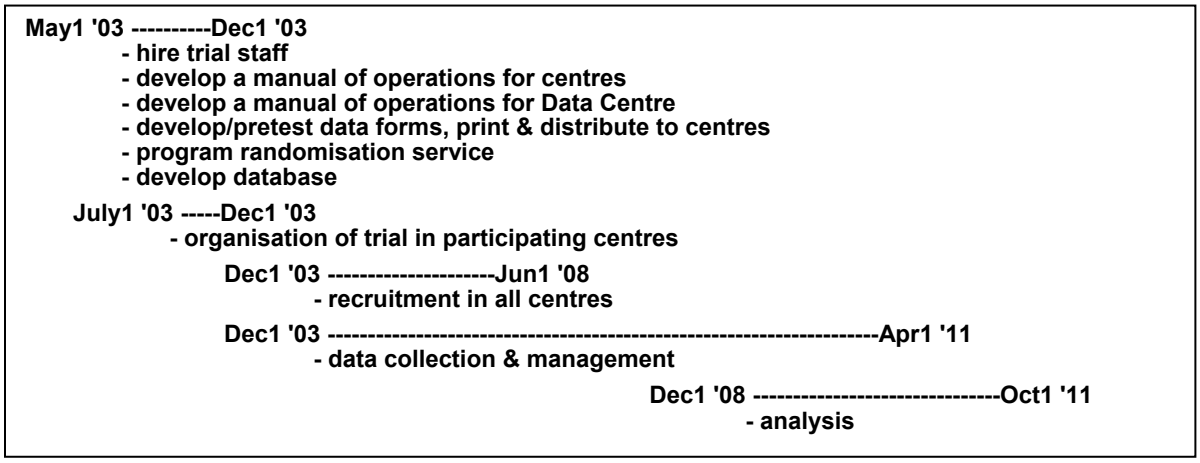
Barrett is the Principal Investigator and is responsible for the progress and timely completion of the trial. Barrett, Armson, Leduc, Hutton and Okun are responsible for responding to clinical queries, visiting sites, and for encouraging recruitment, protocol compliance and accurate and complete data collection. Hannah (the MIRU Director) is responsible for the work of the Data Co-ordinating Centre, including the distribution of funds, the administration of the study, and for providing advice based on previous experiences with the co-ordination of multicentre RCTs. Farrell is responsible for providing advice on the assessments of incontinence. Allen and Ohlsson are responsible for providing advice on the neonatal outcomes. Asztalos is responsible for providing advice on the neurodevelopmental assessments. Joseph is responsible for providing advice on methodological issues and for assisting with posthoc secondary analyses of the dataset. Willan, Barrett and Hannah (the MIRU Director) are responsible for the statistical analyses. Gafni, Barrett, Hannah (the MIRU Director) and Ross are responsible for the economic analyses. All applicants are responsible for assisting with recruitment efforts, including participation in collaborators' meetings, being advocates for the study locally, nationally, and internationally, visiting collaborating centres and attending scientific meetings to present the study results when appropriate.

3.3. Describe the trial Steering Committee and the DSMB

The Steering Committee is responsible for the conduct of the study. The Steering Committee, which includes all applicants, the MIRU Research Manager (Hewson) and the Trial Staff, meets every 2-3 months. A consumer (Julia Hanigsberg) has also joined the Steering Committee. Four members of the Steering Committee (Barrett, Armson, Allen, Asztalos) will form an adjudication subcommittee to review the primary outcomes, masked to allocation group and method of delivery, to confirm that they have or have not occurred. The DSMB, which includes Dr Michael Bracken, Professor, Department of Epidemiology and Public Health, Yale University School of Medicine (chair); Dr Lelia Duley, Resource Centre for Randomised Trials, Nuffield Department of Clinical Medicine, University of Oxford; Dr Jon Tyson, Professor, Department of Pediatrics, University of Texas Health Science Center at Dallas; Prof Allan Donner, Chair, Department of Epidemiology and Biostatistics, The University of Western Ontario; Dr Patricia Crowley, Department of Obstetrics and Gynaecology, Coombe Women's Hospital; will be responsible for the review of the interim analysis and for recommending early termination of the study, if necessary, to the Steering Committee. The trial will be conducted according to the Good Clinical Practice guidelines. [60]

3.4. Timetable for the study

Baseline information will be transmitted to the Data Centre during the randomisation telephone call. Outcome and other descriptive data will be collected on NCR paper forms and mailed to the Data Centre. Data will be scanned into a 'TELEform' data management system. 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 &/or completion.



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