This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities  Page 8
- Long-term follow-up 3 years after discharge  Page 13
- Process flowchart  Page 19
- Contact with women  Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in
the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to
evaluate five specific aspects of caesarean section technique to help determine which
methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women
world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages
and disadvantages of the different options for the conduct of caesarean sections for mother
and baby. The objectives of CORONIS are to determine whether there are any differences
in maternal morbidity when comparing the following five pairs of alternative surgical
techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be
able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in
the hospitals where the caesarean section takes place except on the interventions to be
evaluated.

Eligibility
Women CAN be recruited to CORONIS if:

- They are undergoing delivery by lower segment caesarean section through a
  transverse abdominal incision, irrespective of fever in labour, gestational age or
  whether they have a multiple pregnancy.

Women CANNOT be recruited if:

- there is a clear indication for a particular surgical technique or suture material to be
  used that prevents any of the allocated interventions being used.
  e.g. for a woman with a previous vertical abdominal incision it maybe
  considered inappropriate to do a transverse abdominal incision for this
  caesarean section. However, if a transverse incision is going to be
  performed the woman is eligible.

- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT
All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome
Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise
Clinical
1. Death

2. Febrile morbidity
   *Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.*

3. Endometritis
   *Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.*

4. Wound infection treated with antibiotics
   *Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.*
5. Operative procedures on wound  
*Note:* this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.

6. Pain  
*Note:* this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)  
*Note:* this is defined as women who (a) require additional uterotonics over and above routine, (b) where a brace suture is used (e.g., B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.

9. Stillbirth after trial entry  
*Note:* it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity  
*Note:* this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.

**Health Service Utilisation**

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)
The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:

- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)

Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:

- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites

Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:

- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

Women CAN be recruited to CORONIS if:
• they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
• there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used. e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
they have had more than one previous caesarean section.
they have already been recruited to the trial during a previous pregnancy

2. **On admission**

When a woman is admitted to hospital, she should be given a copy of the leaflet "Information for women having a caesarean section", and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. **Consent**

Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
- that consent is being sought for her participation in a randomised controlled trial
- the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
- that the aspects being compared will be allocated randomly
- that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
- that one hospital visit or home visit is required at six weeks after the birth of her baby
- that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. **Randomising a woman into the study**

- Fill in the *At Study Entry* page of the Data Collection Booklet (you will be asked to give this information over the telephone).

- Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.

  - During the day, staff in the Regional Trial Office will do the randomisation on-line.
  - During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

- During the day, staff in the Regional Trial Office will do the randomisation on-line.
- During the night you will connect to the CORONIS automatic telephone system.

You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.)

• Give the information from the At Study Entry page of the Data Collection Booklet.

• Write down the allocated number in the appropriate box on the At Study Entry page.

• Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete

• Complete allocation boxes on the At Study Entry page.
• Collect **three** sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. **Contents of Allocation Envelope**
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. **Sutures**
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

- Drawer 1 - Polyglactin-910 sutures
- Drawer 2 - Chromic Catgut sutures
- Drawer 3 - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

- The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture **should not** be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. **Surgery**
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the 'Unused sutures' drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. **Data collection**
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used
The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:

- hospital appointment at six weeks after discharge for a routine check-up
- interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
**Error:** The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

### Long term follow-up at 3 years after discharge

Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. **The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment.** The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

### 10. Data queries, missing or inconsistent data resolution

The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

```
CORONIS Data Collection Booklet
Missing or Incorrect Information

These errors/omissions/inconsistencies were found on the Data Collection Booklet for the Study Number shown below. Please could you supply the information or state if it is not known and return this form to the Regional Trial Office as soon as possible. Thank you.

KENYATTA NATIONAL HOSPITAL

Study Number 0132    Hospital record number: 1675678    Randomised on: 08-Mar-2007

After Delivery and Surgical Techniques

1. What was the time of the operation? ………………… 12:24…………………………………………………………

13a. Suture material used for uterine repair is different from allocation, please give reason. ………………………………… Ticked wrong box, vicryl used………………………………

Signed: …………………………… A. J. Banks………………………………………… Date: 04/04/07
```
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in **RED**, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data **MUST** also be written on the site copy of the relevant form in the appropriate place in **RED** pen. The corrected data **MUST** be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

Please only complete pages 3-5 if a Caesarean section was performed - details to be completed by surgeon immediately after surgery.

1. **Actual date and time of start of Caesarean section (knife to skin):**
   - [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
   - [ ] [ ] [ ] [ ] [ ] [ ] [ ]
   - [ ] [ ] [ ] [ ] [ ] [ ] [ ]

2. **Type of anaesthesia (tick all that apply):**
   - Local
   - Spinal
   - Epidural
   - General

3. **Method of emptying bladder prior to surgery:**
   - ‘in out’ catheterisation
   - In-dwelling catheter for the duration

10. **Removal of placenta:**
    - Controlled cord traction
    - Manual removal
    - Other
    - If Other, please specify:

11. **Was the uterine cavity swabbed after delivery of the placenta?**
    - Yes
    - No

11. **Transfer of a woman recruited in your hospital to other hospitals (or wards)**
If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

   (i) your name and the hospital you are calling from
   (ii) CORONIS Study Number
   (iii) the woman’s name
   (iv) the woman’s date of birth
   (v) the name of hospital to which the woman is being transferred
   (vi) the name of the receiving obstetrician / clinician

12. **Serious Adverse Event Reporting**
Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

We would, however, expect the following to be reported:

- Severe haemorrhage (requiring transfusion of six units or more of blood)
- Repeat laparotomy
- Hysterectomy
- Peritonitis
Deep venous thrombosis  
Curettage of uterus  
Internal iliac artery or other major artery ligation  
Brace suture (e.g. B-Lynch suture)  
Balloon tamponade  
Uterine packing  
Pulmonary embolism  
Septicaemia  
Any severe or unexpected morbidity should be reported.

13. Trial Monitoring
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
OBTAINING CONSENT

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?

Yes

Woman is NOT eligible for the CORONIS Trial

Has the woman had more than one previous caesarean section?

Has the woman been recruited to the trial before?

Yes

Woman is NOT eligible for the CORONIS Trial

No

(See protocol for further details)

Is there a clear indication for a particular surgical technique to be used?

Yes

Woman is NOT eligible for the CORONIS Trial

No

Collect an Information for Women leaflet and Consent form from CORONIS box

Talk to woman about the CORONIS trial (see Obtaining Informed Consent guide)

Has the woman agreed to participate in the CORONIS Trial?

No

Reassure woman this will not effect her treatment and treat as required

Yes

Woman signs Consent form (there are 3 copies)

Copy 1

Give the woman the top copy of the Consent Form and an 'Information for Women' leaflet

Copy 2

File the blue copy of the Consent Form in the Document Box

Copy 3

Fax or send the pink copy of the Consent Form to the Regional Trial Office
Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Is a particular suture material specified on the allocation?

Yes
Take 3 packs of allocated sutures from the CORONIS suture box
Place sutures in notes to go to theatre with the woman

No
Put Allocation Form and DCB in the woman’s notes to go to theatre

IT IS IMPORTANT to make the call as close to surgery time as possible
**BEFORE SURGERY**

Remove the *Allocation Form* from woman's notes and place in clear view of surgeon.

Is a particular suture material specified in the allocation?

- **Yes**
  - Make suture available to surgeon

- **No**
  - Return unused sutures to the CORONIS suture box

Conduct surgery as specified on *Allocation Form*.

Return *Allocation Form* to *DCB* in woman's notes.

**AFTER SURGERY**

Collect a *Medical card* and complete with woman's name, date of birth, study number and appointment date.

Take *DCB* from woman's notes.

Complete page 2 of the *DCB*.

Give woman her *Medical Card*.

Ensure surgeon completes pages 3-5 of the *DCB* and return to the woman's notes.

Complete all data forms using a black pen. All questions must be answered.
AT DISCHARGE FROM HOSPITAL

Collect DCB from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

Complete all data forms using a black pen. All questions must be answered

SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP

Where will the woman be seen at 6-weeks post-discharge?

At the hospital?

At a local clinic?

At home?

By phone?

Organise 6-week follow-up before woman is discharged and put date on Medical card

Put DCB in woman’s notes

Inform RTO that woman needs to be followed-up at home or by phone

RTO organise 6-week visit to the woman’s home / telephone call to complete Six Week Form

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

Key

Instruction

Question

Option or note
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of **ALL** women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section **AFTER DELIVERY**

**Parity:**
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age ≥24 weeks), including the baby delivered as part of the CORONIS Trial.

**Best estimate of gestational age:**
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

**Planned trial of scar:**
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

**Duration of Caesarean section procedure:**
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section **POSTPARTUM STAY IN HOSPITAL**

**Operative procedures on wound:**
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

**Severe or unexpected maternal events:**
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   Phone +44 1865 289750, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   Send a text message to +44 07944876799
   Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>
   A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   Send an email to coronis@npeu.ox.ac.uk, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   Send a fax to +44 1865 289740, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**
   If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**
   If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**
   If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**
   If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:

   - Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
   - Inform the RTO staff of the error. They will collect the unused envelope from you.
   - Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
Handbook for Participating Sites

February 2008
Version 7
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities Page 8
- Long-term follow-up 3 years after discharge Page 13
- Process flowchart Page 19
- Contact with women Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to evaluate five specific aspects of caesarean section technique to help determine which methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women worldwide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages and disadvantages of the different options for the conduct of caesarean sections for mother and baby. The objectives of CORONIS are to determine whether there are any differences in maternal morbidity when comparing the following five pairs of alternative surgical techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in the hospitals where the caesarean section takes place except on the interventions to be evaluated.

Eligibility
Women CAN be recruited to CORONIS if:
- They are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
- there is a clear indication for a particular surgical technique or suture material to be used that prevents any of the allocated interventions being used, e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT

All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome

Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise

Clinical

1. Death

2. Febrile morbidity
   *Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.*

3. Endometritis
   *Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.*

4. Wound infection treated with antibiotics
   *Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.*
5. Operative procedures on wound

Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.

6. Pain

Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)

Note: this is defined as women who (a) require additional uterotonics over and above routine, (b) where a brace suture is used (e.g., B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.

9. Stillbirth after trial entry

Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity

Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.

Health Service Utilisation

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)
The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:
- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)
Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:
- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites
Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:
- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

Women CAN be recruited to CORONIS if:
• they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
• there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used. e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
2. **On admission**

When a woman is admitted to hospital, she should be given a copy of the leaflet "Information for women having a caesarean section", and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. **Consent**

Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
- that consent is being sought for her participation in a randomised controlled trial
- the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
- that the aspects being compared will be allocated randomly
- that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
- that one hospital visit or home visit is required at six weeks after the birth of her baby
- that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. **Randomising a woman into the study**

- Fill in the *At Study Entry* page of the Data Collection Booklet (you will be asked to give this information over the telephone).

- Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.

- During the day, staff in the Regional Trial Office will do the randomisation on-line.
- During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.)

Give the information from the At Study Entry page of the Data Collection Booklet.

Write down the allocated number in the appropriate box on the At Study Entry page.

Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete

- Complete allocation boxes on the At Study Entry page.
• Collect three sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. Contents of Allocation Envelope
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. Sutures
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

- Drawer 1 - Polyglactin-910 sutures
- Drawer 2 - Chromic Catgut sutures
- Drawer 3 - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

- The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture should not be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. Surgery
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the ‘Unused sutures’ drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. Data collection
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used
The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:
- hospital appointment at six weeks after discharge for a routine check-up
- interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
Error: The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

Long term follow-up at 3 years after discharge
Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment. The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

10. Data queries, missing or inconsistent data resolution
The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

<table>
<thead>
<tr>
<th>CORONIS Data Collection Booklet Missing or Incorrect Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>These errors/omissions/inconsistencies were found on the Data Collection Booklet for the Study Number shown below. Please could you supply the information or state if it is not known and return this form to the Regional Trial Office as soon as possible. Thank you.</td>
</tr>
<tr>
<td>KENYATTA NATIONAL HOSPITAL</td>
</tr>
<tr>
<td>Study Number 0132</td>
</tr>
<tr>
<td>Hospital record number: 1675678</td>
</tr>
<tr>
<td>Randomised on: 08-Mar-2007</td>
</tr>
<tr>
<td>After Delivery and Surgical Techniques</td>
</tr>
<tr>
<td>1. What was the time of the operation? 12:24</td>
</tr>
<tr>
<td>13a. Suture material used for uterine repair is different from allocation, please give reason. Ticked wrong box, vicryl used</td>
</tr>
<tr>
<td>Signed: A. J. Banks Date: 04/04/07</td>
</tr>
</tbody>
</table>
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in RED, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data MUST also be written on the site copy of the relevant form in the appropriate place in RED pen. The corrected data MUST be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

Please only complete pages 3-5 if a Caesarean section was performed - details to be completed by surgeon immediately after surgery.

1. **Actual date and time of start of Caesarean section (knife to skin):**
   - Day: 12
   - Month: 5
   - Year: 2008

2. **Type of anaesthesia** (tick all that apply):
   - Local
   - Spinal
   - Epidural
   - General

3. **Method of emptying bladder prior to surgery:**
   - ‘in out’ catheterisation
   - Indwelling catheter for the duration

4. **Removal of placenta:**
   - Controlled cord traction
   - Manual removal
   - Other

5. **If Other, please specify:**
   - [ ]

6. **Was the uterine cavity swabbed after delivery of the placenta?**
   - Yes [ ] No [ ]

   **AJB 04/04/7**

11. **Transfer of a woman recruited in your hospital to other hospitals (or wards)**
   If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

   (i) your name and the hospital you are calling from
   (ii) CORONIS Study Number
   (iii) the woman’s name
   (iv) the woman’s date of birth
   (v) the name of hospital to which the woman is being transferred
   (vi) the name of the receiving obstetrician / clinician

12. **Serious Adverse Event Reporting**
   Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

   We would, however, expect the following to be reported:
   - Severe haemorrhage (requiring transfusion of six units or more of blood)
   - Repeat laparotomy
   - Hysterectomy
   - Peritonitis
Deep venous thrombosis
Curettage of uterus
Internal iliac artery or other major artery ligation
Brace suture (e.g. B-Lynch suture)
Balloon tamponade
Uterine packing
Pulmonary embolism
Septicaemia
Any severe or unexpected morbidity should be reported.

13. Trial Monitoring
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
**OBTAINING CONSENT**

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?  
Yes → Woman is NOT eligible for the CORONIS Trial  
No → Has the woman had more than one previous caesarean section?  
Yes → Woman is NOT eligible for the CORONIS Trial  
No → (See protocol for further details)

Is there a clear indication for a particular surgical technique to be used?  
Yes → Woman is NOT eligible for the CORONIS Trial  
No → Collect an *Information for Women* leaflet and *Consent* form from CORONIS box

Talk to woman about the CORONIS trial (see *Obtaining Informed Consent* guide)

Has the woman agreed to participate in the CORONIS Trial?  
No → Reassure woman this will not effect her treatment and treat as required  
Yes → Woman signs *Consent* form (there are 3 copies)

Copy 1 → Give the woman the top copy of the *Consent Form* and an ‘*Information for Women*’ leaflet  
Copy 2 → File the blue copy of the *Consent Form* in the Document Box  
Copy 3 → Fax or send the pink copy of the *Consent Form* to the Regional Trial Office
AT STUDY ENTRY

Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Is a particular suture material specified on the allocation?

Yes

Take 3 packs of allocated sutures from the CORONIS suture box

Place sutures in notes to go to theatre with the woman

No

Put Allocation Form and DCB in the woman’s notes to go to theatre

IT IS IMPORTANT to make the call as close to surgery time as possible

IT IS IMPORTANT to make the call as close to surgery time as possible
BEFORE SURGERY

Remove the Allocation Form from woman’s notes and place in clear view of surgeon.

Is a particular suture material specified in the allocation?
- **Yes**: Make suture available to surgeon.
- **No**: Conduct surgery as specified on Allocation Form.

Return Allocation Form to DCB in woman’s notes.

AFTER SURGERY

Collect a Medical card and complete with woman’s name, date of birth, study number and appointment date.

Take DCB from woman’s notes.

Complete page 2 of the DCB.

Give woman her Medical Card.

Ensure surgeon completes pages 3-5 of the DCB and return to the woman’s notes.

Complete all data forms using a black pen. All questions must be answered.

Return unused sutures to the CORONIS suture box.
AT DISCHARGE FROM HOSPITAL

Collect DCB from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

Complete all data forms using a black pen. All questions must be answered

SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP

Where will the woman be seen at 6-weeks post-discharge?

At the hospital?

At a local clinic?

At home?

By phone?

Organise 6-week follow-up before woman is discharged and put date on Medical card

Put DCB in woman’s notes

Inform RTO that woman needs to be followed-up at home or by phone

RTO organise 6-week visit to the woman’s home / telephone call to complete Six Week Form

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

Key

Instruction

Question

Option or note
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY
Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age ≥ 24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL
Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   - Phone +44 1865 289750, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   - Send a text message to +44 07944876799
   - Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>
   - A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   - Send an email to coronis@npeu.ox.ac.uk, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   - Send a fax to +44 1865 289740, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**
   If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**
   If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**
   If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**
   If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:

   - Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
   - Inform the RTO staff of the error. They will collect the unused envelope from you.
   - Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities
- Long-term follow-up 3 years after discharge
- Process flowchart
- Contact with women
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to evaluate five specific aspects of caesarean section technique to help determine which methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages and disadvantages of the different options for the conduct of caesarean sections for mother and baby. The objectives of CORONIS are to determine whether there are any differences in maternal morbidity when comparing the following five pairs of alternative surgical techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in the hospitals where the caesarean section takes place except on the interventions to be evaluated.

Eligibility
Women CAN be recruited to CORONIS if:
- They are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
- there is a clear indication for a particular surgical technique or suture material to be used that prevents any of the allocated interventions being used.
  e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT

All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome
Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise

Clinical

1. Death

2. Febrile morbidity
   Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.

3. Endometritis
   Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.

4. Wound infection treated with antibiotics
   Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.
5. Operative procedures on wound
   Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.

6. Pain
   Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)
   Note: this is defined as women who (a) require additional uterotonic over and above routine, (b) where a brace suture is used (e.g., B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.

9. Stillbirth after trial entry
   Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity
   Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.

Health Service Utilisation

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)
The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:
• recruitment of participating sites via the Regional Co-ordinators
• distribution and supply of trial documentation and materials to the Regional Trial Offices
• providing on-site training for all RTO staff
• providing a 24 hour randomisation system via the internet or a telephony system
• central data management
• data cleaning
• data analysis
• collection and dissemination of adverse event data
• site monitoring - annually
• central financial management
• organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
• organising regular investigators meetings

Regional Trial Offices (RTO)
Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:
• distribution and supply of trial documentation and materials to participating sites
• coordinate documentation of training undertaken by operators in each of the participating sites
• on-line randomisation of women into the trial (using the telephony system out of working hours)
• local data management
• data entry and cleaning
• collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
• organise local meetings of participating doctors and midwives

Participating sites
Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:
• be familiar with the trial
• liaise with their Regional Trial Office
• ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria
   
   **Women CAN be recruited to CORONIS if:**
   • they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, *irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.*

   **Women CANNOT be recruited if:**
   • there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used.
     
     e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
• they have had more than one previous caesarean section.
• they have already been recruited to the trial during a previous pregnancy

2. On admission
When a woman is admitted to hospital, she should be given a copy of the leaflet “Information for women having a caesarean section”, and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. Consent
Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
• that consent is being sought for her participation in a randomised controlled trial
• the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
• that the aspects being compared will be allocated randomly
• that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
• that one hospital visit or home visit is required at six weeks after the birth of her baby
• that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. Randomising a woman into the study
• Fill in the At Study Entry page of the Data Collection Booklet (you will be asked to give this information over the telephone).

• Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.

- During the day, staff in the Regional Trial Office will do the randomisation on-line.
- During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.)

Give the information from the At Study Entry page of the Data Collection Booklet.

Write down the allocated number in the appropriate box on the At Study Entry page.

Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete
• Complete allocation boxes on the At Study Entry page.
• Collect three sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. Contents of Allocation Envelope
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. Sutures
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

Drawer 1 - Polyglactin-910 sutures
Drawer 2 - Chromic Catgut sutures
Drawer 3 - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

• The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture should not be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. Surgery
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the ‘Unused sutures’ drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. Data collection
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used
The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:
• hospital appointment at six weeks after discharge for a routine check-up
• interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
Error: The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

Long term follow-up at 3 years after discharge
Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment. The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

10. Data queries, missing or inconsistent data resolution
The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

<table>
<thead>
<tr>
<th>CORONIS Data Collection Booklet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing or Incorrect Information</td>
</tr>
</tbody>
</table>

These errors/omissions/inconsistencies were found on the Data Collection Booklet for the Study Number shown below. Please could you supply the information or state if it is not known and return this form to the Regional Trial Office as soon as possible. Thank you.

KENYATTA NATIONAL HOSPITAL

Study Number   0132    Hospital record number: 1675678    Randomised on: 08-Mar-2007

After Delivery and Surgical Techniques

1. What was the time of the operation? …………………12:24………………………………………………………………………..

13a. Suture material used for uterine repair is different from allocation, please give reason. ………………………………….Ticked wrong box, vicryl used……………………………..

Signed: ………………………………….A. J. Banks…………………………………………….. Date: 04/04/07
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in **RED**, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data **MUST** also be written on the site copy of the relevant form in the appropriate place in **RED** pen. The corrected data **MUST** be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

Please only complete pages 3-5 if a Caesarean section was performed - details to be completed by surgeon immediately after surgery.

1. **Actual date and time of start of Caesarean section (knife to skin):**
   - [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
   - [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
   - [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
   - [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

2. **Type of anaesthesia** (tick all that apply):
   - Local
   - Spinal
   - Epidural
   - General

3. **Method of emptying bladder prior to surgery:**
   - ‘in out’ catheterisation
   - In-dwelling catheter for the duration

10. **Removal of placenta:**
    - Controlled cord traction
    - Manual removal
    - Other

   If Other, please specify:

11. **Was the uterine cavity swabbed after delivery of the placenta?**
    - [ ] Yes
    - [ ] No

**AJB 04/04/7**

11. **Transfer of a woman recruited in your hospital to other hospitals (or wards)**
If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

   (i) your name and the hospital you are calling from
   (ii) CORONIS Study Number
   (iii) the woman’s name
   (iv) the woman’s date of birth
   (v) the name of hospital to which the woman is being transferred
   (vi) the name of the receiving obstetrician / clinician

12. **Serious Adverse Event Reporting**
Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

We would, however, expect the following to be reported:

- Severe haemorrhage (requiring transfusion of six units or more of blood)
- Repeat laparotomy
- Hysterectomy
- Peritonitis
Deep venous thrombosis
Curettage of uterus
Internal iliac artery or other major artery ligation
Brace suture (e.g. B-Lynch suture)
Balloon tamponade
Uterine packing
Pulmonary embolism
Septicaemia
Any severe or unexpected morbidity should be reported.

13. Trial Monitoring
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
OBTAINING CONSENT

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?

Yes

Has the woman had more than one previous caesarean section?

Yes

Woman is NOT eligible for the CORONIS Trial

No

Has the woman been recruited to the trial before?

No

Is there a clear indication for a particular surgical technique to be used?

Yes

Woman is NOT eligible for the CORONIS Trial

No

Collect an Information for Women leaflet and Consent form from CORONIS box

Talk to woman about the CORONIS trial (see Obtaining Informed Consent guide)

Has the woman agreed to participate in the CORONIS Trial?

No

Reassure woman this will not effect her treatment and treat as required

Yes

Woman signs Consent form (there are 3 copies)

Copy 1

Give the woman the top copy of the Consent Form and an 'Information for Women' leaflet

Copy 2

File the blue copy of the Consent Form in the Document Box

Copy 3

Fax or send the pink copy of the Consent Form to the Regional Trial Office

(See protocol for further details)
Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Put Allocation Form and DCB in the woman’s notes to go to theatre

Is a particular suture material specified on the allocation?

Yes

Take 3 packs of allocated sutures from the CORONIS suture box

No

Place sutures in notes to go to theatre with the woman

IT IS IMPORTANT to make the call as close to surgery time as possible
**BEFORE SURGERY**

Remove the *Allocation Form* from woman’s notes and place in clear view of surgeon.

Is a particular suture material specified in the allocation?

- **Yes**
  - Make suture available to surgeon

- **No**
  - Conduct surgery as specified on *Allocation Form*

Return *Allocation Form* to *DCB* in woman’s notes.

**AFTER SURGERY**

Collect a *Medical card* and complete with woman’s name, date of birth, study number and appointment date.

Take *DCB* from woman’s notes.

Complete page 2 of the *DCB*.

Give woman her *Medical Card*.

Ensure surgeon completes pages 3-5 of the *DCB* and return to the woman’s notes.

Complete all data forms using a black pen. All questions must be answered.

Return unused sutures to the CORONIS suture box.
AT DISCHARGE FROM HOSPITAL

Collect DCB from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

Complete all data forms using a black pen. All questions must be answered

SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP

Where will the woman be seen at 6-weeks post-discharge?

- At the hospital?
- At a local clinic?
- At home?
- By phone?

Organise 6-week follow-up before woman is discharged and put date on Medical card

Put DCB in woman’s notes

Inform RTO that woman needs to be followed-up at home or by phone

RTO organise 6-week visit to the woman’s home / telephone call to complete Six Week Form

When pages 10-12 are complete, following the 6 week appointment, remove top copies from DCB and fax or send to the RTO

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

Key

- Instruction
- Question
- Option or note
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY

Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age >24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL

Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   Phone +44 1865 289750, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   Send a text message to +44 07944876799
   Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>
   A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   Send an email to coronis@npeu.ox.ac.uk, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   Send a fax to +44 1865 289740, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**  
If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**  
If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**  
If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**  
If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**  
If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:

- Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
- Inform the RTO staff of the error. They will collect the unused envelope from you.
- Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**  
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**  
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**  
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**  
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
NOTES (for your use)
Handbook for Participating Sites

February 2008
Version 7
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities Page 8
- Long-term follow-up 3 years after discharge Page 13
- Process flowchart Page 19
- Contact with women Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to evaluate five specific aspects of caesarean section technique to help determine which methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages and disadvantages of the different options for the conduct of caesarean sections for mother and baby. The objectives of CORONIS are to determine whether there are any differences in maternal morbidity when comparing the following five pairs of alternative surgical techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in the hospitals where the caesarean section takes place except on the interventions to be evaluated.

Eligibility
Women CAN be recruited to CORONIS if:
- They are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
- there is a clear indication for a particular surgical technique or suture material to be used that prevents any of the allocated interventions being used. 
  e.g. for a woman with a previous vertical abdominal incision it maybe considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT
All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome
Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise
Clinical
1. Death

2. Febrile morbidity
   *Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.*

3. Endometritis
   *Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.*

4. Wound infection treated with antibiotics
   *Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.*
5. Operative procedures on wound  
*Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.*

6. Pain  
*Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.*

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)  
*Note: this is defined as women who (a) require additional uterotonic over and above routine, (b) where a brace suture is used (e.g., B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.*

9. Stillbirth after trial entry  
*Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.*

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity  
*Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.*

Health Service Utilisation

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)
The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:
- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)
Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:
- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites
Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:
- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

Women CAN be recruited to CORONIS if:
• they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
• there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used.
  e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
2. **On admission**

When a woman is admitted to hospital, she should be given a copy of the leaflet “Information for women having a caesarean section”, and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. **Consent**

Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:

- that consent is being sought for her participation in a randomised controlled trial
- the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
- that the aspects being compared will be allocated randomly
- that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
- that one hospital visit or home visit is required at six weeks after the birth of her baby
- that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. **Randomising a woman into the study**

- Fill in the *At Study Entry* page of the Data Collection Booklet (you will be asked to give this information over the telephone).

- Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.

  - During the day, staff in the Regional Trial Office will do the randomisation on-line.
  - During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

•• •• You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.).

• Give the information from the At Study Entry page of the Data Collection Booklet.

• Write down the allocated number in the appropriate box on the At Study Entry page.

• Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete
• Complete allocation boxes on the At Study Entry page.
• Collect three sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. Contents of Allocation Envelope
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. Sutures
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

   Drawer 1 - Polyglactin-910 sutures
   Drawer 2 - Chromic Catgut sutures
   Drawer 3 - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

• The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture should not be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. Surgery
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the ‘Unused sutures’ drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. Data collection
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used
The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:
• hospital appointment at six weeks after discharge for a routine check-up
• interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
Error: The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

Long term follow-up at 3 years after discharge
Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment. The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

10. Data queries, missing or inconsistent data resolution
The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

<table>
<thead>
<tr>
<th>CORONIS Data Collection Booklet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing or Incorrect Information</td>
</tr>
</tbody>
</table>

These errors/omissions/inconsistencies were found on the Data Collection Booklet for the Study Number shown below. Please could you supply the information or state if it is not known and return this form to the Regional Trial Office as soon as possible. Thank you.

KENYATTA NATIONAL HOSPITAL

Study Number 0132 Hospital record number: 1675678 Randomised on: 08-Mar-2007

After Delivery and Surgical Techniques
1. What was the time of the operation? ……………………………………………………………………………………12:24…………………………………………………………………………………..

13a. Suture material used for uterine repair is different from allocation, please give reason. ………………………………….Ticked wrong box, vicryl used……………………………………………………

Signed: ……………………………A. J. Banks…………………………………………. Date: 04/04/07
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in RED, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data MUST also be written on the site copy of the relevant form in the appropriate place in RED pen. The corrected data MUST be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

Please only complete pages 3-5 if a Caesarean section was performed - details to be completed by surgeon immediately after surgery.

1. Actual date and time of start of Caesarean section (knife to skin):
   - [ ] Day / [ ] Month / [ ] Year
   - [ ] Hours / [ ] Minutes

2. Type of anaesthesia (tick all that apply):
   - Local
   - Spinal
   - Epidural
   - General

3. Method of emptying bladder prior to surgery:
   - ‘in out’ catheterisation
   - In-dwelling catheter for the duration

10. Removal of placenta:
   - Controlled cord traction
   - Manual removal
   - Other
   - If Other, please specify:

11. Was the uterine cavity swabbed after delivery of the placenta?
   - Yes [ ]
   - No [ ]
   - AJB 04/04/7

11. Transfer of a woman recruited in your hospital to other hospitals (or wards)

   If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

   (i) your name and the hospital you are calling from
   (ii) CORONIS Study Number
   (iii) the woman’s name
   (iv) the woman’s date of birth
   (v) the name of hospital to which the woman is being transferred
   (vi) the name of the receiving obstetrician / clinician

12. Serious Adverse Event Reporting

   Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

   We would, however, expect the following to be reported:

   Severe haemorrhage (requiring transfusion of six units or more of blood)
   Repeat laparotomy
   Hysterectomy
   Peritonitis
Deep venous thrombosis
Curettage of uterus
Internal iliac artery or other major artery ligation
Brace suture (e.g. B-Lynch suture)
Balloon tamponade
Uterine packing
Pulmonary embolism
Septicaemia
Any severe or unexpected morbidity should be reported.

13. Trial Monitoring
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
OBTAINING CONSENT

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?

Yes

Has the woman had more than one previous caesarean section?
Has the woman been recruited to the trial before?

Yes

Has there a clear indication for a particular surgical technique to be used?

Yes

No

Collect an Information for Women leaflet and Consent form from CORONIS box

Talk to woman about the CORONIS trial (see Obtaining Informed Consent guide)

Has the woman agreed to participate in the CORONIS Trial?

Yes

Woman signs Consent form (there are 3 copies)

Copy 1

Give the woman the top copy of the Consent Form and an 'Information for Women' leaflet

Copy 2

File the blue copy of the Consent Form in the Document Box

Copy 3

Fax or send the pink copy of the Consent Form to the Regional Trial Office

No

Woman is NOT eligible for the CORONIS Trial

Yes

No

No

No

No

Reassure woman this will not effect her treatment and treat as required

(See protocol for further details)
Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Is a particular suture material specified on the allocation?

Yes

Take 3 packs of allocated sutures from the CORONIS suture box

No

Place sutures in notes to go to theatre with the woman

Put Allocation Form and DCB in the woman’s notes to go to theatre

IT IS IMPORTANT to make the call as close to surgery time as possible

AT STUDY ENTRY
**BEFORE SURGERY**

Remove the *Allocation Form* from woman’s notes and place in clear view of surgeon

- Is a particular suture material specified in the allocation?
  - Yes → Make suture available to surgeon
  - No → Conduct surgery as specified on *Allocation Form*

Return *Allocation Form* to *DCB* in woman’s notes

**AFTER SURGERY**

Collect a *Medical card* and complete with woman’s name, date of birth, study number and appointment date

- Take *DCB* from woman’s notes
- Complete page 2 of the *DCB*
- Give woman her *Medical Card*
- Ensure surgeon completes pages 3-5 of the *DCB* and return to the woman’s notes

Complete all data forms using a black pen. All questions must be answered.
**AT DISCHARGE FROM HOSPITAL**

Collect *DCB* from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

Complete all data forms using a black pen. All questions must be answered

**SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP**

**Where will the woman be seen at 6-weeks post-discharge?**

- **At the hospital?**
  - Yes → Organise 6-week follow-up before woman is discharged and put date on *Medical card*
  - No → At a local clinic?
    - Yes → Put *DCB* in woman’s notes
    - No → At home?
      - Yes → By phone?
        - Yes → Inform RTO that woman needs to be followed-up at home or by phone
        - No → RTO organise 6-week visit to the woman's home / telephone call to complete *Six Week Form*
      - No → All data entered at the RTO and any queries clarified with recruiting centre / doctor

- **Inform RTO that woman needs to be followed-up at home or by phone**

- **RTO organise 6-week visit to the woman's home / telephone call to complete *Six Week Form***

- **Organise regular contact with women to ensure long-term follow-up at 3 years post discharge**

**Key**

- **Instruction**
- **Question**
- **Option or note**
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY
Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age ≥24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL
Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   Phone +44 1865 289750, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   Send a text message to +44 07944876799
   Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>
   A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   Send an email to coronis@npeu.ox.ac.uk, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   Send a fax to +44 1865 289740, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**
   If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**
   If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**
   If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**
   If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:

   - Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
   - Inform the RTO staff of the error. They will collect the unused envelope from you.
   - Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
Handbook for Participating Sites

February 2008
Version 7
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities
  - Page 8
- Long-term follow-up 3 years after discharge
  - Page 13
- Process flowchart
  - Page 19
- Contact with women
  - Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to evaluate five specific aspects of caesarean section technique to help determine which methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages and disadvantages of the different options for the conduct of caesarean sections for mother and baby. The objectives of CORONIS are to determine whether there are any differences in maternal morbidity when comparing the following five pairs of alternative surgical techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in the hospitals where the caesarean section takes place except on the interventions to be evaluated.

Eligibility
Women CAN be recruited to CORONIS if:
- They are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
- there is a clear indication for a particular surgical technique or suture material to be used that prevents any of the allocated interventions being used.
  e.g. for a woman with a previous vertical abdominal incision it maybe considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT
All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome
Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise
Clinical
1. Death

2. Febrile morbidity
Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.

3. Endometritis
Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.

4. Wound infection treated with antibiotics
Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.
5. Operative procedures on wound  
*Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.*

6. Pain  
*Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.*

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)  
*Note: this is defined as women who (a) require additional uterotonics over and above routine, (b) where a brace suture is used (e.g.. B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.*

9. Stillbirth after trial entry  
*Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.*

10. Apgar score ≤ 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity  
*Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.*

**Health Service Utilisation**

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)
The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:
- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)
Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:
- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites
Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:
- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

Women CAN be recruited to CORONIS if:
• they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
• there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used. e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
• they have had more than one previous caesarean section.
• they have already been recruited to the trial during a previous pregnancy

2. On admission
When a woman is admitted to hospital, she should be given a copy of the leaflet “Information for women having a caesarean section”, and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. Consent
Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
• that consent is being sought for her participation in a randomised controlled trial
• the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
• that the aspects being compared will be allocated randomly
• that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
• that one hospital visit or home visit is required at six weeks after the birth of her baby
• that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. Randomising a woman into the study
• Fill in the At Study Entry page of the Data Collection Booklet (you will be asked to give this information over the telephone).

• Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.

- During the day, staff in the Regional Trial Office will do the randomisation on-line.
- During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

- You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.)

- Give the information from the At Study Entry page of the Data Collection Booklet.

- Write down the allocated number in the appropriate box on the At Study Entry page.

- Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete
• Complete allocation boxes on the At Study Entry page.
• Collect three sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. Contents of Allocation Envelope
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. Sutures
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

- Drawer 1 - Polyglactin-910 sutures
- Drawer 2 - Chromic Catgut sutures
- Drawer 3 - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

- The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture should not be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. Surgery
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the ‘Unused sutures’ drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. Data collection
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

**At Study Entry**
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the *At Study Entry* page of the Data Collection Booklet (DCB).

**Immediately After Delivery**
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

**Note:** Question one, page 2: Parity; this should include the delivery that has just taken place.

**Surgical Techniques Used**
The surgeon should complete this section (pages 3-5) immediately after surgery.

**Postpartum Hospital Stay**
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

**Six Weeks After Discharge**
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:
- hospital appointment at six weeks after discharge for a routine check-up
- interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
**Error:** The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

**Long term follow-up at 3 years after discharge**
Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. **The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment.** The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

**10. Data queries, missing or inconsistent data resolution**
The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Hospital record number</th>
<th>Randomised on</th>
</tr>
</thead>
<tbody>
<tr>
<td>0132</td>
<td>1675678</td>
<td>08-Mar-2007</td>
</tr>
</tbody>
</table>

**After Delivery and Surgical Techniques**

1. What was the time of the operation? ……………..12:24………………………………………………………………………………

13a. Suture material used for uterine repair is different from allocation, please give reason. ………………………………….Ticked wrong box, vicryl used…………………………

Signed: ……………………………A. J. Banks.…………………………………… Date: 04/04/07
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in **RED**, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data **MUST** also be written on the site copy of the relevant form in the appropriate place in **RED** pen. The corrected data **MUST** be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

<table>
<thead>
<tr>
<th>Study Number</th>
<th>0 1 3 2</th>
</tr>
</thead>
</table>

1. **Actual date and time of start of Caesarean section (knife to skin):**
   - [ ] / [ ] / [ ] [ ] [ ] [ ]
   - (DAY / MONTH / YEAR)

2. **Type of anaesthesia** (tick all that apply):
   - [ ] Local
   - [ ] Spinal
   - [ ] Epidural
   - [ ] General

3. **Method of emptying bladder prior to surgery:**
   - [ ] ‘in out’ catheterisation
   - [ ] In-dwelling catheter for the duration

4. **Removal of placenta:**
   - [ ] Controlled cord traction
   - [ ] Manual removal
   - [ ] Other

5. **If Other, please specify:**
   - [ ]

6. **Was the uterine cavity swabbed after delivery of the placenta?**
   - [ ] Yes
   - [ ] No

---

11. **Transfer of a woman recruited in your hospital to other hospitals (or wards)**

   If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

   (i) your name and the hospital you are calling from
   (ii) CORONIS Study Number
   (iii) the woman’s name
   (iv) the woman’s date of birth
   (v) the name of hospital to which the woman is being transferred
   (vi) the name of the receiving obstetrician / clinician

12. **Serious Adverse Event Reporting**

    Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

    We would, however, expect the following to be reported:

    Severe haemorrhage (requiring transfusion of six units or more of blood)
    Repeat laparotomy
    Hysterectomy
    Peritonitis
Deep venous thrombosis
Curettage of uterus
Internal iliac artery or other major artery ligation
Brace suture (e.g. B-Lynch suture)
Balloon tamponade
Uterine packing
Pulmonary embolism
Septicaemia
Any severe or unexpected morbidity should be reported.

13. Trial Monitoring
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
OBTAINING CONSENT

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision? 

Yes \(\rightarrow\) 

Woman is NOT eligible for the CORONIS Trial

No \(\rightarrow\) 

Has the woman had more than one previous caesarean section? Has the woman been recruited to the trial before? 

Yes \(\rightarrow\) 

Woman is NOT eligible for the CORONIS Trial

No \(\rightarrow\) 

Is there a clear indication for a particular surgical technique to be used? 

Yes \(\rightarrow\) 

Woman is NOT eligible for the CORONIS Trial

No \(\rightarrow\) 

Collect an Information for Women leaflet and Consent form from CORONIS box

Talk to woman about the CORONIS trial (see Obtaining Informed Consent guide)

Has the woman agreed to participate in the CORONIS Trial? 

Yes \(\rightarrow\) 

Woman signs Consent form (there are 3 copies) 

Reassure woman this will not effect her treatment and treat as required

No \(\rightarrow\) 

Give the woman the top copy of the Consent Form and an ‘Information for Women’ leaflet

File the blue copy of the Consent Form in the Document Box

Fax or send the pink copy of the Consent Form to the Regional Trial Office
Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Is a particular suture material specified on the allocation?  
  Yes
  Take 3 packs of allocated sutures from the CORONIS suture box
  Place sutures in notes to go to theatre with the woman

  No
  Put Allocation Form and DCB in the woman’s notes to go to theatre

IT IS IMPORTANT to make the call as close to surgery time as possible
BEFORE SURGERY

Remove the Allocation Form from woman’s notes and place in clear view of surgeon

Is a particular suture material specified in the allocation?

Yes

Make suture available to surgeon

No

Conduct surgery as specified on Allocation Form

Return Allocation Form to DCB in woman’s notes

AFTER SURGERY

Collect a Medical card and complete with woman’s name, date of birth, study number and appointment date

Take DCB from woman’s notes

Complete page 2 of the DCB

Give woman her Medical Card

Ensure surgeon completes pages 3-5 of the DCB and return to the woman’s notes

Complete all data forms using a black pen. All questions must be answered

Return unused sutures to the CORONIS suture box
**AT DISCHARGE FROM HOSPITAL**

Collect *DCB* from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

**SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP**

Where will the woman be seen at 6-weeks post-discharge?

- At the hospital? **Yes**
- At a local clinic? **Yes**
- At home? **Yes**
- By phone? **Yes**

Organise 6-week follow-up before woman is discharged and put date on *Medical card*

Put *DCB* in woman’s notes

Inform RTO that woman needs to be followed-up at home or by phone

When pages 10-12 are complete, following the 6 week appointment, remove top copies from *DCB* and fax or send to the RTO

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

---

**Key**

- Instruction
- Question
- Option or note

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CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY
Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age >24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL
Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. By telephone:
   Phone +44 1865 289750, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. By text message:
   Send a text message to +44 07944876799
   Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>
   A member of the Co-ordinating Centre staff will call you back.

3. By sending an Email:
   Send an email to coronis@npeu.ox.ac.uk, include a telephone number so we can call you and an outline of the problem you have encountered.

4. By fax:
   Send a fax to +44 1865 289740, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**
   If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**
   If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**
   If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**
   If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:

   - Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
   - Inform the RTO staff of the error. They will collect the unused envelope from you.
   - Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**  
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**  
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**  
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**  
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
CORONIS
International study of caesarean section surgical techniques: a randomised factorial trial

Handbook for Participating Sites

February 2008
Version 7
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities  Page 8
- Long-term follow-up 3 years after discharge  Page 13
- Process flowchart  Page 19
- Contact with women  Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to evaluate five specific aspects of caesarean section technique to help determine which methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages and disadvantages of the different options for the conduct of caesarean sections for mother and baby. The objectives of CORONIS are to determine whether there are any differences in maternal morbidity when comparing the following five pairs of alternative surgical techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in the hospitals where the caesarean section takes place except on the interventions to be evaluated.

Eligibility
Women CAN be recruited to CORONIS if:
   • They are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
   • there is a clear indication for a particular surgical technique or suture material to be used that prevents any of the allocated interventions being used.  
   e.g. for a woman with a previous vertical abdominal incision it maybe considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
   • they have had more than one previous caesarean section.
   • they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT

All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome

Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise

Clinical

1. Death

2. Febrile morbidity
   Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.

3. Endometritis
   Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.

4. Wound infection treated with antibiotics
   Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.
5. Operative procedures on wound  
*Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.*

6. Pain  
*Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of 'severe pain' will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.*

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)  
*Note: this is defined as women who (a) require additional uterotonic over and above routine, (b) where a brace suture is used (e.g., B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.*

9. Stillbirth after trial entry  
*Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.*

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity  
*Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.*

**Health Service Utilisation**

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)
The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:
- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)
Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:
- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites
Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:
- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

Women CAN be recruited to CORONIS if:
• they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
• there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used. e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
they have had more than one previous caesarean section.
they have already been recruited to the trial during a previous pregnancy

2. On admission
When a woman is admitted to hospital, she should be given a copy of the leaflet “Information for women having a caesarean section”, and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. Consent
Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
• that consent is being sought for her participation in a randomised controlled trial
• the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
• that the aspects being compared will be allocated randomly
• that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
• that one hospital visit or home visit is required at six weeks after the birth of her baby
• that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. Randomising a woman into the study
• Fill in the At Study Entry page of the Data Collection Booklet (you will be asked to give this information over the telephone).

• Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.

- During the day, staff in the Regional Trial Office will do the randomisation on-line.
- During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

- You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.)

- Give the information from the At Study Entry page of the Data Collection Booklet.

- Write down the allocated number in the appropriate box on the At Study Entry page.

- Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete
• Complete allocation boxes on the At Study Entry page.
• Collect three sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. Contents of Allocation Envelope
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. Sutures
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

- Drawer 1 - Polyglactin-910 sutures
- Drawer 2 - Chromic Catgut sutures
- Drawer 3 - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

• The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture should not be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. Surgery
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the ‘Unused sutures’ drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. Data collection
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used
The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:

- hospital appointment at six weeks after discharge for a routine check-up
- interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
Error: The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE.  Thank you

Long term follow-up at 3 years after discharge
Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. **The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment.** The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

10. Data queries, missing or inconsistent data resolution
The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

<table>
<thead>
<tr>
<th>CORONIS Data Collection Booklet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing or Incorrect Information</td>
</tr>
</tbody>
</table>

**KENYATTA NATIONAL HOSPITAL**

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Hospital record number: 1675678</th>
<th>Randomised on: 08-Mar-2007</th>
</tr>
</thead>
</table>

**After Delivery and Surgical Techniques**

1. What was the time of the operation? ………………………………………12:24…………………………………………………………………………………………

13a. Suture material used for uterine repair is different from allocation, please give reason. ……………………………………………………………………Ticked wrong box, vicryl used……………………………………

Signed: …………………………… A. J. Banks. ……………………………………… Date: 04/04/07
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in RED, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data MUST also be written on the site copy of the relevant form in the appropriate place in RED pen. The corrected data MUST be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

| Study Number | 0 1 3 2 |

1. **This page only complete pages 3-5 if a Caesarean section was performed - details to be completed by surgeon immediately after surgery.**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Actual date and time of start of Caesarean section (knife to skin):</td>
</tr>
<tr>
<td>2</td>
<td>Type of anaesthesia (tick all that apply): Local, Spinal, Epidural, General</td>
</tr>
<tr>
<td>3</td>
<td>Method of emptying bladder prior to surgery: 'in out' catheterisation, in-dwelling catheter for the duration</td>
</tr>
<tr>
<td>10</td>
<td>Removal of placenta: Controlled cord traction, Manual removal, Other</td>
</tr>
<tr>
<td>11</td>
<td>Was the uterine cavity swabbed after delivery of the placenta? Yes ☑️ No ☑️ AJB 04/04/7</td>
</tr>
</tbody>
</table>

11. **Transfer of a woman recruited in your hospital to other hospitals (or wards)**

If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

(i) your name and the hospital you are calling from
(ii) CORONIS Study Number
(iii) the woman’s name
(iv) the woman’s date of birth
(v) the name of hospital to which the woman is being transferred
(vi) the name of the receiving obstetrician / clinician

12. **Serious Adverse Event Reporting**

Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

We would, however, expect the following to be reported:

- Severe haemorrhage (requiring transfusion of six units or more of blood)
- Repeat laparotomy
- Hysterectomy
- Peritonitis
Deep venous thrombosis  
Curettage of uterus  
Internal iliac artery or other major artery ligation  
Brace suture (e.g. B-Lynch suture)  
Balloon tamponade  
Uterine packing  
Pulmonary embolism  
Septicaemia  
Any severe or unexpected morbidity should be reported.

13. **Trial Monitoring**  
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
**OBTAINING CONSENT**

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?
- Yes
- No

Has the woman had more than one previous caesarean section?
- Yes
- No

Has the woman been recruited to the trial before?
- Yes
- No

Is there a clear indication for a particular surgical technique to be used?
- Yes
- No

Collect an *Information for Women* leaflet and *Consent* form from CORONIS box

Talk to woman about the CORONIS trial (see *Obtaining Informed Consent* guide)

Has the woman agreed to participate in the CORONIS Trial?
- Yes
- No

Woman signs *Consent* form (there are 3 copies)

Give the woman the top copy of the *Consent Form* and an ‘*Information for Women*’ leaflet

File the blue copy of the *Consent Form* in the Document Box

Fax or send the pink copy of the *Consent Form* to the Regional Trial Office

(See protocol for further details)
Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Is a particular suture material specified on the allocation?

Yes

Take 3 packs of allocated sutures from the CORONIS suture box

Place sutures in notes to go to theatre with the woman

No

Put Allocation Form and DCB in the woman’s notes to go to theatre

IT IS IMPORTANT to make the call as close to surgery time as possible
BEFORE SURGERY

Remove the *Allocation Form* from woman’s notes and place in clear view of surgeon

Is a particular suture material specified in the allocation?

Yes → Make suture available to surgeon

No → Conduct surgery as specified on *Allocation Form*

Return *Allocation Form* to *DCB* in woman’s notes

AFTER SURGERY

Collect a *Medical card* and complete with woman’s name, date of birth, study number and appointment date

Take *DCB* from woman’s notes

Complete page 2 of the *DCB*

Give woman her *Medical Card*

Ensure surgeon completes pages 3-5 of the *DCB* and return to the woman’s notes

Complete all data forms using a black pen. All questions must be answered

Return unused sutures to the CORONIS suture box
AT DISCHARGE FROM HOSPITAL

Collect DCB from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

Complete all data forms using a black pen. All questions must be answered

SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP

Where will the woman be seen at 6-weeks post-discharge?

- At the hospital?
- At a local clinic?
- At home?
- By phone?

Organise 6-week follow-up before woman is discharged and put date on Medical card

Put DCB in woman’s notes

Inform RTO that woman needs to be followed-up at home or by phone

RTO organise 6-week visit to the woman’s home / telephone call to complete Six Week Form

When pages 10-12 are complete, following the 6 week appointment, remove top copies from DCB and fax or send to the RTO

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

Key
- Instruction
- Question
- Option or note
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY

Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age ≥24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL

Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   Phone +44 1865 289750, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   Send a text message to +44 07944876799
   Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORonis STUDY>
   A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   Send an email to coronis@npeu.ox.ac.uk, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   Send a fax to +44 1865 289740, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**
   If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**
   If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**
   If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**
   If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:
   - Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
   - Inform the RTO staff of the error. They will collect the unused envelope from you.
   - Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**  
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**  
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**  
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**  
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tube ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
NOTES (for your use)
Handbook for Participating Sites

February 2008
Version 7
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities Page 8
- Long-term follow-up 3 years after discharge Page 13
- Process flowchart Page 19
- Contact with women Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in
the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to
evaluate five specific aspects of caesarean section technique to help determine which
methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women
world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages
and disadvantages of the different options for the conduct of caesarean sections for mother
and baby. The objectives of CORONIS are to determine whether there are any differences
in maternal morbidity when comparing the following five pairs of alternative surgical
techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be
able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in
the hospitals where the caesarean section takes place except on the interventions to be
evaluated.

Eligibility
Women CAN be recruited to CORONIS if:
- They are undergoing delivery by lower segment caesarean section through a
  transverse abdominal incision, irrespective of fever in labour, gestational age or
  whether they have a multiple pregnancy.

Women CANNOT be recruited if:
- there is a clear indication for a particular surgical technique or suture material to be
  used that prevents any of the allocated interventions being used.  
  e.g. for a woman with a previous vertical abdominal incision it may be
  considered inappropriate to do a transverse abdominal incision for this
  caesarean section. However, if a transverse incision is going to be
  performed the woman is eligible.
- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT

All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome

Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise

Clinical

1. Death

2. Febrile morbidity
   Note: any clinical diagnosis of fever $>38^\circ C$ made by a health professional and treated with antibiotics during postnatal hospital stay.

3. Endometritis
   Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.

4. Wound infection treated with antibiotics
   Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.
5. Operative procedures on wound
Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.

6. Pain
Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)
Note: this is defined as women who (a) require additional uterotonics over and above routine, (b) where a brace suture is used (e.g.. B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.

9. Stillbirth after trial entry
Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity
Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.

Health Service Utilisation

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)
The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:
- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)
Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:
- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites
Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:
- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

Women CAN be recruited to CORONIS if:
• they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
• there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used. e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
• they have had more than one previous caesarean section.
• they have already been recruited to the trial during a previous pregnancy

2. On admission
When a woman is admitted to hospital, she should be given a copy of the leaflet “Information for women having a caesarean section”, and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. Consent
Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
• that consent is being sought for her participation in a randomised controlled trial
• the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
• that the aspects being compared will be allocated randomly
• that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
• that one hospital visit or home visit is required at six weeks after the birth of her baby
• that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. Randomising a woman into the study
• Fill in the At Study Entry page of the Data Collection Booklet (you will be asked to give this information over the telephone).

• Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.
  
  - During the day, staff in the Regional Trial Office will do the randomisation on-line.
  - During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

• You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.).

• Give the information from the At Study Entry page of the Data Collection Booklet.

• Write down the allocated number in the appropriate box on the At Study Entry page.

• Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete
  • Complete allocation boxes on the At Study Entry page.
• Collect **three** sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. **Contents of Allocation Envelope**
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. **Sutures**
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

- **Drawer 1** - Polyglactin-910 sutures
- **Drawer 2** - Chromic Catgut sutures
- **Drawer 3** - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

• **The lead Clinician in each participating site is responsible for monitoring this process.**
  **The RTO will check routinely that this process is being adhered to.**

Regardless of the suture material allocated, any unused suture should not be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. **Surgery**
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the 'Unused sutures' drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. **Data collection**
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used
The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:
• hospital appointment at six weeks after discharge for a routine check-up
• interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
Error: The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

Long term follow-up at 3 years after discharge
Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment. The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

10. Data queries, missing or inconsistent data resolution
The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Hospital record number</th>
<th>Randomised on</th>
</tr>
</thead>
<tbody>
<tr>
<td>0132</td>
<td>1675678</td>
<td>08-Mar-2007</td>
</tr>
</tbody>
</table>

After Delivery and Surgical Techniques

1. What was the time of the operation? ……………………12:24………………………………………………………………………………

13a. Suture material used for uterine repair is different from allocation, please give reason. …………………………….Ticked wrong box, vicryl used…………………………

Signed: …………………………….A. J. Banks………………………………………… Date: 04/04/07
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in **RED**, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data **MUST** also be written on the site copy of the relevant form in the appropriate place in **RED** pen. The corrected data **MUST** be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

Please only complete pages 3-5 if a Caesarean section was performed - details to be completed by surgeon immediately after surgery.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Actual date and time of start of Caesarean section (knife to skin):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Type of anaesthesia (tick all that apply):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>Spinal</td>
<td>Epidural</td>
<td>General</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Method of emptying bladder prior to surgery:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘in out’ catheterisation</td>
<td>in-dwelling catheter for the duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Removal of placenta:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled cord traction</td>
<td>Manual removal</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Was the uterine cavity swabbed after delivery of the placenta?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**11. Transfer of a woman recruited in your hospital to other hospitals (or wards)**

If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

(i) your name and the hospital you are calling from
(ii) CORONIS Study Number
(iii) the woman’s name
(iv) the woman’s date of birth
(v) the name of hospital to which the woman is being transferred
(vi) the name of the receiving obstetrician / clinician

**12. Serious Adverse Event Reporting**

Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

We would, however, expect the following to be reported:

- Severe haemorrhage (requiring transfusion of six units or more of blood)
- Repeat laparotomy
- Hysterectomy
- Peritonitis
Deep venous thrombosis
Curettage of uterus
Internal iliac artery or other major artery ligation
Brace suture (e.g. B-Lynch suture)
Balloon tamponade
Uterine packing
Pulmonary embolism
Septicaemia
Any severe or unexpected morbidity should be reported.

13. Trial Monitoring
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
**OBTAINING CONSENT**

- Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?
  - Yes: **Woman is NOT eligible for the CORONIS Trial**
  - No: **Talk to woman about the CORONIS trial (see Obtaining Informed Consent guide)**

- Has the woman had more than one previous caesarean section? Has the woman been recruited to the trial before?
  - Yes: **Woman is NOT eligible for the CORONIS Trial**
  - No: **Is there a clear indication for a particular surgical technique to be used?**
    - Yes: **Woman is NOT eligible for the CORONIS Trial**
    - No: **Collect an Information for Women leaflet and Consent form from CORONIS box**

- Talk to woman about the CORONIS trial (see Obtaining Informed Consent guide)

- Has the woman agreed to participate in the CORONIS Trial?
  - Yes: **Woman signs Consent form (there are 3 copies)**
  - No: **Reassure woman this will not effect her treatment and treat as required**

- **Copy 1**
  - Give the woman the top copy of the Consent Form and an 'Information for Women' leaflet

- **Copy 2**
  - File the blue copy of the Consent Form in the Document Box

- **Copy 3**
  - Fax or send the pink copy of the Consent Form to the Regional Trial Office
Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Is a particular suture material specified on the allocation?

Yes
Take 3 packs of allocated sutures from the CORONIS suture box

No
Place sutures in notes to go to theatre with the woman

Put Allocation Form and DCB in the woman’s notes to go to theatre

IT IS IMPORTANT to make the call as close to surgery time as possible
**BEFORE SURGERY**

Remove the *Allocation Form* from woman’s notes and place in clear view of surgeon

Is a particular suture material specified in the allocation?

- **Yes**
  - Make suture available to surgeon
  - Conduct surgery as specified on *Allocation Form*

- **No**
  - Return unused sutures to the CORONIS suture box
  - Conduct surgery as specified on *Allocation Form*

Return *Allocation Form* to *DCB* in woman’s notes

**AFTER SURGERY**

Collect a *Medical card* and complete with woman’s name, date of birth, study number and appointment date

- Take *DCB* from woman’s notes
- Complete page 2 of the *DCB*
- Give woman her *Medical Card*
- Ensure surgeon completes pages 3-5 of the *DCB* and return to the woman’s notes

Complete all data forms using a black pen. All questions must be answered
AT DISCHARGE FROM HOSPITAL

Collect DCB from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

Complete all data forms using a black pen. All questions must be answered

SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP

Where will the woman be seen at 6-weeks post-discharge?

Yes

At the hospital?

Yes

Organise 6-week follow-up before woman is discharged and put date on Medical card

Put DCB in woman’s notes

When pages 10-12 are complete, following the 6 week appointment, remove top copies from DCB and fax or send to the RTO

Inform RTO that woman needs to be followed-up at home or by phone

RTO organise 6-week visit to the woman’s home / telephone call to complete Six Week Form

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

Key

Instruction

Question

Option or note
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY
Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age >24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL
Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   Phone +44 1865 289750, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   Send a text message to +44 07944876799
   Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>
   A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   Send an email to coronis@npeu.ox.ac.uk, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   Send a fax to +44 1865 289740, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**
   If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**
   If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**
   If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**
   If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:

   - Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
   - Inform the RTO staff of the error. They will collect the unused envelope from you.
   - Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
CORONIS
International study of caesarean section surgical techniques: a randomised factorial trial

Handbook for Participating Sites

February 2008
Version 7
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities Page 8
- Long-term follow-up 3 years after discharge Page 13
- Process flowchart Page 19
- Contact with women Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to evaluate five specific aspects of caesarean section technique to help determine which methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages and disadvantages of the different options for the conduct of caesarean sections for mother and baby. The objectives of CORONIS are to determine whether there are any differences in maternal morbidity when comparing the following five pairs of alternative surgical techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in the hospitals where the caesarean section takes place except on the interventions to be evaluated.

Eligibility
Women CAN be recruited to CORONIS if:

- They are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:

- there is a clear indication for a particular surgical technique or suture material to be used that prevents any of the allocated interventions being used.
  e.g. for a woman with a previous vertical abdominal incision it maybe considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT

All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome
Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise
Clinical
1. Death

2. Febrile morbidity
   Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.

3. Endometritis
   Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.

4. Wound infection treated with antibiotics
   Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.
5. Operative procedures on wound  
*Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.*

6. Pain  
*Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.*

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)  
*Note: this is defined as women who (a) require additional uterotonics over and above routine, (b) where a brace suture is used (e.g., B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.*

9. Stillbirth after trial entry  
*Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.*

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity  
*Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.*

**Health Service Utilisation**

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)

The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:

- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)

Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:

- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites

Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:

- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

- Protocol
- Handbook for Participating Sites
- Information for Women
- Guidance on Obtaining Informed Consent
- Consent Forms
- CORONIS stickers for hospital notes & Medical Cards
- Data Collection Booklets (DCB)
- Serious Adverse Event Forms
- Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
- Training material: DVD, Training log-book, Certificates for approved operators
- Trial awareness material: CORONIS posters and handouts
- Envelopes
- CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

   Women CAN be recruited to CORONIS if:
   - they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

   Women CANNOT be recruited if:
   - there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used. e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
• they have had more than one previous caesarean section.
• they have already been recruited to the trial during a previous pregnancy

2. **On admission**
When a woman is admitted to hospital, she should be given a copy of the leaflet "**Information for women having a caesarean section**", and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. **Consent**
Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
• that consent is being sought for her participation in a randomised controlled trial
• the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
• that the aspects being compared will be allocated randomly
• that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
• that one hospital visit or home visit is required at six weeks after the birth of her baby
• that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. **Randomising a woman into the study**
• Fill in the **At Study Entry** page of the Data Collection Booklet (you will be asked to give this information over the telephone).

• Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit), the call is a local number or a FREEPHONE number depending on where your site is.
  - During the day, staff in the Regional Trial Office will do the randomisation on-line.
  - During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone, takes about 3 minutes. [The automated telephone system is in three languages. You will be asked which language you require.]

- You will be asked for your hospital and doctor code before randomisation can proceed. (You will be given this information at the beginning of the study. If, at any time, you forget these codes you must call the RTO and they will have the information available.)

- Give the information from the At Study Entry page of the Data Collection Booklet.

- Write down the allocated number in the appropriate box on the At Study Entry page.

- Open the Allocation Envelope corresponding to the 4 digit number given over the telephone.

5. When randomisation is complete
• Complete allocation boxes on the At Study Entry page.
• Collect three sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. Contents of Allocation Envelope
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. Sutures
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

- Drawer 1 - Polyglactin-910 sutures
- Drawer 2 - Chromic Catgut sutures
- Drawer 3 - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

• The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture should not be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. Surgery
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the ‘Unused sutures’ drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. Data collection
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital

The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry

Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery

As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used

The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay

During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge

All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:

- hospital appointment at six weeks after discharge for a routine check-up
- interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
**Error:** The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

**Long term follow-up at 3 years after discharge**

Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. **The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment.** The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

**10. Data queries, missing or inconsistent data resolution**

The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

---

**CORONIS Data Collection Booklet**

**Missing or Incorrect Information**

These errors/omissions/inconsistencies were found on the Data Collection Booklet for the Study Number shown below. Please could you supply the information or state if it is not known and return this form to the Regional Trial Office as soon as possible. Thank you.

KENYATTA NATIONAL HOSPITAL

Study Number 0132 Hospital record number: 1675678 Randomised on: 08-Mar-2007

After Delivery and Surgical Techniques

1. What was the time of the operation? …………………12:24………………………………………………………………………

13a. Suture material used for uterine repair is different from allocation, please give reason. …………………………………. Ticked wrong box, vicryl used…………………………

Signed: ……………………………A. J. Banks………………………………………… Date: 04/04/07

---
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in **RED**, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data **MUST** also be written on the site copy of the relevant form in the appropriate place in **RED** pen. The corrected data **MUST** be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

Please only complete pages 3-5 if a Caesarean section was performed - details to be completed by surgeon immediately after surgery.

1. Actual date and time of start of Caesarean section (knife to skin):
   - [ ] [ ] [ ] [ ] [ ] [ ]
   - [ ] [ ] [ ] [ ] [ ] [ ]

2. Type of anaesthesia (tick all that apply):
   - [ ] Local
   - [ ] Spinal
   - [ ] Epidural
   - [ ] General

3. Method of emptying bladder prior to surgery:
   - [ ] ‘in out’ catheterisation
   - [ ] in-dwelling catheter for the duration

10. Removal of placenta:
   - [ ] Controlled cord traction
   - [ ] Manual removal
   - [ ] Other
   - [ ] If Other, please specify:

11. Was the uterine cavity swabbed after delivery of the placenta?
   - [ ] Yes
   - [ ] No
   - [ ] AJB 04/04/7

11. **Transfer of a woman recruited in your hospital to other hospitals (or wards)**
If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

   (i) your name and the hospital you are calling from
   (ii) CORONIS Study Number
   (iii) the woman’s name
   (iv) the woman’s date of birth
   (v) the name of hospital to which the woman is being transferred
   (vi) the name of the receiving obstetrician / clinician

12. **Serious Adverse Event Reporting**
Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

We would, however, expect the following to be reported:

- Severe haemorrhage (requiring transfusion of six units or more of blood)
- Repeat laparotomy
- Hysterectomy
- Peritonitis
Deep venous thrombosis
Curettage of uterus
Internal iliac artery or other major artery ligation
Brace suture (e.g. B-Lynch suture)
Balloon tamponade
Uterine packing
Pulmonary embolism
Septicaemia
Any severe or unexpected morbidity should be reported.

13. **Trial Monitoring**
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
OBTAINING CONSENT

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?

Yes → Woman is NOT eligible for the CORONIS Trial

Has the woman had more than one previous caesarean section?

Has the woman been recruited to the trial before?

No → Woman is NOT eligible for the CORONIS Trial

Yes → Has the woman agreed to participate in the CORONIS Trial?

No → Reassure woman this will not effect her treatment and treat as required

Yes → Woman signs Consent form (there are 3 copies)

Copy 1: Give the woman the top copy of the Consent Form and an 'Information for Women' leaflet

Copy 2: File the blue copy of the Consent Form in the Document Box

Copy 3: Fax or send the pink copy of the Consent Form to the Regional Trial Office

(See protocol for further details)
Complete the ‘At Study Entry’ section of the **DCB** BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the *Allocation Form*

Enter the details from the *Allocation Form* in the space provided on the ‘At Study Entry’ section of the **DCB**

Place ‘This woman is in the **CORONIS Trial**’ sticker on the outside of her notes

**Is a particular suture material specified on the allocation?**

**Yes**

Take 3 packs of allocated sutures from the **CORONIS** suture box

Place sutures in notes to go to theatre with the woman

**No**

Put *Allocation Form* and **DCB** in the woman’s notes to go to theatre

**IT IS IMPORTANT** to make the call as close to surgery time as possible
**BEFORE SURGERY**

1. Remove the *Allocation Form* from woman's notes and place in clear view of surgeon.

2. Is a particular suture material specified in the allocation?
   - **Yes**: Make suture available to surgeon.
   - **No**: Conduct surgery as specified on *Allocation Form*.

3. Return *Allocation Form* to DCB in woman's notes.

**AFTER SURGERY**

1. Collect a *Medical card* and complete with woman's name, date of birth, study number and appointment date.

2. Take *DCB* from woman's notes.

3. Complete page 2 of the *DCB*.

4. Give woman her *Medical Card*.

5. Ensure surgeon completes pages 3-5 of the *DCB* and return to the woman's notes.

Complete all data forms using a black pen. All questions must be answered.
AT DISCHARGE FROM HOSPITAL

Collect DCB from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

Complete all data forms using a black pen. All questions must be answered

SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP

Where will the woman be seen at 6-weeks post-discharge?

- At the hospital?
- At a local clinic?
- At home?
- By phone?

Organise 6-week follow-up before woman is discharged and put date on Medical card

Put DCB in woman's notes

Inform RTO that woman needs to be followed-up at home or by phone

RTO organise 6-week visit to the woman's home / telephone call to complete Six Week Form

When pages 10-12 are complete, following the 6 week appointment, remove top copies from DCB and fax or send to the RTO

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

Key
- Instruction
- Question
- Option or note
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY
Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age >24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL
Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   Phone **+44 1865 289750**, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   Send a text message to **+44 07944876799**
   Give **<YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>**
   A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   Send an email to **coronis@npeu.ox.ac.uk**, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   Send a fax to **+44 1865 289740**, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. A woman is randomised in error
   If a woman is randomised in error, e.g. she has not given consent or has already
delivered prior to the telephone call being made to the Regional Trial Office, send
the completed At Study Entry page to the RTO immediately writing clearly at the
bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any
woman randomised in error will be excluded at the analysis stage but they will be
counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the
randomisation telephone call is made as close to the surgery time as possible.

2. The telephone is out of order
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope
number because the telephone line is unavailable or out of order take the LOWEST
NUMBERED envelope (first envelope in the box). Complete the At Study Entry
page with the number of the envelope you have taken and send it IMMEDIATELY to
the RTO. It is very important you inform RTO staff so the numbered envelope that
you have taken is not allocated to another woman.

3. The RTO cannot connect to the internet
   If you telephone the RTO and the internet connection is unavailable you will be
asked to give the woman’s study entry details. The RTO staff will phone you back
when the randomisation is complete with the number of the envelope to take for that
woman. Complete the At Study Entry page with the number of the envelope you
have been allocated and send it IMMEDIATELY to the RTO.

4. The allocated envelope is missing
   If you have been given an envelope number by the RTO staff and when you go to
get it from the Allocation Envelope Box it is missing, you should take the LOWEST
NUMBERED envelope (first envelope in the box). Complete the At Study Entry
page with the number of the envelope you have taken and send it IMMEDIATELY to
the RTO. Inform the RTO that you have been unable to use the allocated envelope
so they can investigate where it may have gone and update the system accordingly.

5. Wrong numbered envelope is taken
   If you take the wrong numbered envelope by mistake you must record on the At
Study Entry page the number of the envelope you have used in error, then:

   • Remove the numbered envelope that was allocated by the RTO staff from the
     envelope box.
   • Inform the RTO staff of the error. They will collect the unused envelope from
     you.
   • Complete the At Study Entry page with the number of the envelope you have
     actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**  
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**  
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**  
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**  
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.
CORONIS
International study of caesarean section surgical
techniques: a randomised factorial trial

Handbook for Participating Sites

February 2008
Version 7
This is Version 7 – February 2008 of the Handbook for Participating Sites.

Changes have been made to the following sections, please read:

- Participating site responsibilities  Page 8
- Long-term follow-up 3 years after discharge  Page 13
- Process flowchart  Page 19
- Contact with women  Page 20
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INTRODUCTION
CORONIS is a fractional factorial randomised controlled trial being conducted in centres in the following six countries: Argentina, Ghana, India, Kenya, Pakistan and Sudan. It aims to evaluate five specific aspects of caesarean section technique to help determine which methods lead to an optimum outcome for women. The trial aims to recruit 15,000 women world-wide between 2007 and 2010.

Existing trials of a similar nature have provided only limited evidence about the advantages and disadvantages of the different options for the conduct of caesarean sections for mother and baby. The objectives of CORONIS are to determine whether there are any differences in maternal morbidity when comparing the following five pairs of alternative surgical techniques undertaken during the time of caesarean section:

1. Blunt versus sharp abdominal entry
2. Exteriorisation of the uterus for repair versus intra-abdominal repair
3. Single versus double layer closure of the uterus
4. Closure versus non-closure of the peritoneum (pelvic and parietal)
5. Chromic catgut versus Polyglactin-910 for uterine repair
   (see protocol for full description of each procedure)

The study is designed to be as simple as possible so that staff in participating sites will be able to recruit women to the study without difficulty and without a large investment of time.

The study will not alter or interfere with any treatment or care given routinely to women in the hospitals where the caesarean section takes place except on the interventions to be evaluated.

Eligibility
Women CAN be recruited to CORONIS if:

- They are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:

- there is a clear indication for a particular surgical technique or suture material to be used that prevents any of the allocated interventions being used. e.g. for a woman with a previous vertical abdominal incision it maybe considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
- they have had more than one previous caesarean section.
- they have already been recruited to the trial during a previous pregnancy.
OTHER ASPECTS OF CLINICAL MANAGEMENT

All other aspects of the operation, apart from those randomly allocated, will be determined by the attending surgeon and anaesthetist including the choice of suture materials and the techniques for repair used.

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of analgesia, perioperative antibiotics or thromboprophylaxis. Current hospital practice should be continued, regardless of participation in the trial.

It is essential that the other aspects of the caesarean section operation remain constant regardless of those aspects which are allocated. So, for example, if it is the usual practice of the surgeon to infiltrate the skin edges with local anaesthetic for post-operative analgesia, this should continue for all women operated on by that surgeon regardless of whether the women is allocated sharp or blunt abdominal entry. The use of other interventions, such as per-rectum analgesia, should similarly be the same for women in each allocated group. Differential use of these co-interventions between randomised groups will render the comparisons of the trial invalid.

OUTCOMES

Primary outcome

Death or maternal infectious morbidity (one or more of the following: antibiotic use for maternal febrile morbidity during postnatal hospital stay, antibiotic use for endometritis, wound infection or peritonitis); or further operative procedures or blood transfusion.

Secondary outcomes – all within 6 weeks of delivery unless stated otherwise

Clinical

1. Death

2. Febrile morbidity
   
   Note: any clinical diagnosis of fever >38°C made by a health professional and treated with antibiotics during postnatal hospital stay.

3. Endometritis
   
   Note: any clinical diagnosis of endometritis made by a health professional and treated with antibiotics during the first six weeks after the caesarean section. For events which occur after discharge from hospital this information will be gathered by interview with each woman six weeks after the caesarean section.

4. Wound infection treated with antibiotics
   
   Note: any antibiotics prescribed specifically for a wound infection. This information will be gathered by interview with each woman at six weeks after the caesarean section.
5. Operative procedures on wound
*Note: this will include any procedures on the wound because of infection, dehiscence or haematoma within the first six weeks following delivery.*

6. Pain
*Note: this will be a subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks. In addition a category of ‘severe pain’ will be recorded if the woman is prescribed additional analgesia over and above routine 24-48 hours after surgery.*

7. Blood transfusion

8. Interventions used for severe primary post-partum haemorrhage (PPH)
*Note: this is defined as women who (a) require additional uterotonic s over and above routine, (b) where a brace suture is used (e.g., B-Lynch suture), (c) where internal iliac artery, or other major artery, ligation is performed, (d) where balloon tamponade or uterine packing is performed or (e) where a hysterectomy is performed.*

9. Stillbirth after trial entry
*Note: it is possible that a delay in abdominal entry associated with different methods may adversely affect neonatal outcome.*

10. Apgar score < 3 at five minutes

11. Laceration of baby at time of caesarean section

12. Death of the baby by six weeks of age

13. Other severe maternal morbidity
*Note: this will include events such as peritonitis, severe secondary post-partum haemorrhage, deep venous thromboses, pulmonary embolism, and sepsis within six weeks of delivery, etc.*

Health Service Utilisation

14. Duration of operation (from incision to closure)

15. Duration of hospital stay post-caesarean section

16. Duration of stay in Intensive Care Unit post-caesarean section

17. Number and duration of re-admissions to hospital within 6 weeks of the caesarean section
CO-ORDINATION OF THE TRIAL

International Co-ordinating Centre (ICC)

The National Perinatal Epidemiology Unit at the University of Oxford is the International Co-ordinating Centre and is responsible for the day-to-day running of the trial.

The functions of the ICC include:
- recruitment of participating sites via the Regional Co-ordinators
- distribution and supply of trial documentation and materials to the Regional Trial Offices
- providing on-site training for all RTO staff
- providing a 24 hour randomisation system via the internet or a telephony system
- central data management
- data cleaning
- data analysis
- collection and dissemination of adverse event data
- site monitoring - annually
- central financial management
- organising and servicing the Data Monitoring Committee and the Trial Steering Committee.
- organising regular investigators meetings

Regional Trial Offices (RTO)

Each region has a trial office with responsibility to the Regional Coordinator. The Regional Trial Office (RTO) is responsible for one or more participating site. The responsibilities of each RTO include:
- distribution and supply of trial documentation and materials to participating sites
- coordinate documentation of training undertaken by operators in each of the participating sites
- on-line randomisation of women into the trial (using the telephony system out of working hours)
- local data management
- data entry and cleaning
- collection of serious adverse event data and communication of this to the International Trial Co-ordinating Centre and elsewhere as required
- organise local meetings of participating doctors and midwives

Participating sites

Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CORONIS Trial in their unit.

The specific responsibility of the local co-ordinators will be to:
- be familiar with the trial
- liaise with their Regional Trial Office
- ensure that all medical and nursing staff involved in the care of pregnant women are well informed about the trial
• ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
• ensure that supplies of Data Collection Booklets are always available, that they are completed and returned to the RTO promptly, and to deal with any queries arising
• notify the RTO of any serious adverse events
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• ensure that sutures are being used appropriately and are always available in sites allocated to evaluate polyglactin-910 vs catgut
• put in place systems for the 6 week follow-up and the 3 year long-term follow-up for all women recruited

TRIAL DOCUMENTATION

The following material forms the trial documentation:

• Protocol
• Handbook for Participating Sites
• Information for Women
• Guidance on Obtaining Informed Consent
• Consent Forms
• CORONIS stickers for hospital notes & Medical Cards
• Data Collection Booklets (DCB)
• Serious Adverse Event Forms
• Six Week After Discharge Forms (this form is also part of the Data Collection Booklet)
• Training material: DVD, Training log-book, Certificates for approved operators
• Trial awareness material: CORONIS posters and handouts
• Envelopes
• CD containing trial documentation can be found in the Trial Master File at the RTO

TRIAL PROCEDURES

1. Identifying women who are eligible - Eligibility criteria

Women CAN be recruited to CORONIS if:
• they are undergoing delivery by lower segment caesarean section through a transverse abdominal incision, irrespective of fever in labour, gestational age or whether they have a multiple pregnancy.

Women CANNOT be recruited if:
• there is a clear indication for a particular surgical technique or material to be used that prevents any of the allocated interventions being used. 
  e.g. for a woman with a previous vertical abdominal incision it may be considered inappropriate to do a transverse abdominal incision for this caesarean section. However, if a transverse incision is going to be performed the woman is eligible.
• they have had more than one previous caesarean section.
• they have already been recruited to the trial during a previous pregnancy

2. On admission
When a woman is admitted to hospital, she should be given a copy of the leaflet "Information for women having a caesarean section", and the possibility that she may become eligible for CORONIS should be discussed. The woman may be approached in the ante-natal clinic if elective surgery is likely to be an option. It is important that the woman is approached and informed consent is gained before she is taken for surgery. Very often an emergency situation arises, therefore it is important that the woman knows about the CORONIS study and can make a quick decision about joining the study should the need arise.

3. Consent
Once a woman becomes eligible i.e. a lower segment caesarean is planned, the study should be discussed with her (and her partner/family as appropriate).

During this discussion the following points should be addressed:
• that consent is being sought for her participation in a randomised controlled trial
• the trial will compare different aspects of caesarean section techniques, all of which are in common practice throughout the world
• that the aspects being compared will be allocated randomly
• that participation in the trial is voluntary and declining to enter the trial will not affect the quality of the medical care she receives
• that one hospital visit or home visit is required at six weeks after the birth of her baby
• that she is free to withdraw from the trial prior to surgery, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the trial

If the woman decides to withdraw from the trial after surgery she should be asked if she will allow information about her stay in hospital to be collected and invited to attend a six week follow-up so that we can see how she is doing. If the woman insists that she does not want her medical information to be recorded for the trial and she insists she will not attend a six week follow-up appointment, her decision should be respected and all contact should cease.

All women are required to sign a formal consent form if they agree to participate in the trial. If women are not able to sign a consent form, the method of recording consent which is currently used in that setting should be used for the trial (for example, the recording of a thumb print from the woman on the consent form). For more information see Process Flowchart, page 16.

4. Randomising a woman into the study
• Fill in the At Study Entry page of the Data Collection Booklet (you will be asked to give this information over the telephone).

• Label hospital notes with a CORONIS sticker to make it easy to see that the woman has been recruited into the study.
• Call the randomisation telephone number (the number will be displayed in your Unit),
the call is a local number or a FREEPHONE number depending on where your site is.
- During the day, staff in the Regional Trial Office will do the randomisation on-line.
- During the night you will connect to the CORONIS automatic telephone system.

Recruiting a woman using the randomisation service, on-line or automated telephone,
takes about 3 minutes. [The automated telephone system is in three languages. You will
be asked which language you require.]

- You will be asked for your hospital and doctor code before randomisation can proceed.
  (You will be given this information at the beginning of the study. If, at any time, you
  forget these codes you must call the RTO and they will have the information available.).

- Give the information from the At Study Entry page of the Data Collection Booklet.

- Write down the allocated number in the appropriate box on the At Study Entry page.

- Open the Allocation Envelope corresponding to the 4 digit number given over the
telephone.

5. When randomisation is complete
• Complete allocation boxes on the At Study Entry page.
• Collect **three** sutures from the CORONIS suture box (if applicable).
• Proceed to perform caesarean section according to the allocation form (see next page).

6. **Contents of Allocation Envelope**
The Allocation Envelope contains an Allocation Form detailing the randomised interventions to be performed.

7. **Sutures**
Not all participating sites will be allocated the suture intervention, those who are will be provided with a Suture Box containing an initial stock of sutures. The box has three drawers:

- **Drawer 1** - Polyglactin-910 sutures
- **Drawer 2** - Chromic Catgut sutures
- **Drawer 3** - Unused sutures

Three sutures of the type indicated on the Allocation Form should be taken from the suture box. Any unused sutures should be returned to the bottom drawer for re-distribution.

• The lead Clinician in each participating site is responsible for monitoring this process. The RTO will check routinely that this process is being adhered to.

Regardless of the suture material allocated, any unused suture **should not** be used to effect repair of any tissue layer other than the uterus. Use of the allocated suture material to close other layers will render the comparison of Polyglactin-910 versus Chromic Catgut invalid. It is therefore very important that the use of sutures is monitored carefully and supplies are maintained.

8. **Surgery**
The Caesarean section must be completed according to the allocations given on the Allocation Form. If the Allocation Form indicates the use of sutures, take three sutures of the appropriate kind from the CORONIS suture box. If all three sutures are not used the remainder should be returned to the ‘Unused sutures’ drawer of the CORONIS suture box.

If at anytime during surgery the surgeon is not able to perform the randomised allocation the reason for deviating from the allocated interventions must be stated in the Data Collection Booklet.

The surgeon must complete the Surgical Techniques Used section (pages 3-5) immediately after surgery.

9. **Data collection**
Information will be collected at the following times:
1. at study entry
2. immediately following surgery
3. at discharge from hospital (including transfer to another hospital or ward)
4. at six weeks after discharge from hospital
The Data Collection Booklet should be completed in black pen. ALL questions should be answered. If Data Collection forms are submitted to the RTO with missing data or data that is inconsistent, the RTO will request the missing data or resolution of any data queries. Always try to complete the forms accurately and completely to ensure that the study can provide reliable data to answer the questions being addressed by CORONIS.

At Study Entry
Information at study entry, including eligibility and maternal characteristics, should be collected from the hospital notes and recorded on the At Study Entry page of the Data Collection Booklet (DCB).

Immediately After Delivery
As soon as delivery is complete, regardless of the actual mode of delivery, information about the delivery should be completed (page 2).

Note: Question one, page 2: Parity; this should include the delivery that has just taken place.

Surgical Techniques Used
The surgeon should complete this section (pages 3-5) immediately after surgery.

Postpartum Hospital Stay
During the woman’s stay in hospital, staff should record all information required on the Postpartum Hospital Stay section (pages 6-9) of the DCB. This information should be obtained from the woman’s hospital records. Complete contact details, including details of the woman’s partner, family and referring doctor if possible.

If you have information that you think maybe relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page and submit it with the DCB to your RTO.

Six Weeks After Discharge
All women will be seen six weeks after discharge from hospital. At this follow-up the final pages of the DCB must be completed (pages 10-12). Six week follow-up can be achieved in a variety of ways:
• hospital appointment at six weeks after discharge for a routine check-up
• interviews by appropriately trained personnel employed by the trial either by home visits or by telephone (if feasible).

Separate Six Weeks After Discharge Forms are provided to be used if the follow-up is being performed outside the hospital, e.g. at home and is being co-ordinated by the RTO.

To facilitate the accurate recording of clinical diagnoses and treatments after hospital discharge, women are provided with a Medical Card to take home. Women should ask health professionals who they see after hospital discharge to record any diagnoses made and record the treatment prescribed. Although this is unlikely to be used on all occasions, it should enhance the quality of the information obtained at the six week interview.
Error: The Yes/No boxes have been omitted on Question 10 of the Six Weeks After Discharge form. If the woman has not been diagnosed with any of the conditions listed please write alongside the boxes NONE. Thank you

Long term follow-up at 3 years after discharge
Sufficient information will be collected about the participating women in the trial to allow further follow-up if funds can be secured in the future. Of particular interest in the future is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, placental problems, subsequent wound complications and stillbirths.

A CORONIS medical document bag containing a letter about the long-term follow-up with contact details of the hospital, a Medical Card and a Change of Address Card should be given to the woman at her six week follow-up visit for safe keeping. The woman should be told to ask each clinician she consults during the following 3 years to complete the Medical Card. This information will assist in the long-term follow-up assessment. The CORONIS systems will provide reminders of the date the women is due for her long-term follow-up visit. Regular contact with the woman during the three year period should be made by the best possible means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

10. Data queries, missing or inconsistent data resolution
The RTO will send a list of data queries, missing or inconsistent data to participating hospital(s) regularly. The list will contain the woman’s Study Number, the date she was recruited into the trial and the information requiring resolution. These queries should be dealt with immediately to avoid hospital notes being unavailable to be reviewed.

The list will look like this:

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Hospital record number:</th>
<th>Randomised on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0132</td>
<td>1675678</td>
<td>08-Mar-2007</td>
</tr>
</tbody>
</table>

After Delivery and Surgical Techniques

1. What was the time of the operation? ……………………………………………………………………………………………

13a. Suture material used for uterine repair is different from allocation, please give reason. …………………………………Ticked wrong box, vicryl used…………………………

Signed: ……………………………A. J. Banks.………………………………………… Date: 04/04/07
The woman’s notes should be reviewed and the correct information ascertained. The correct data should be written on the list in RED, as shown above. The list should be signed and dated and returned to the RTO as soon as possible so that the data records can be completed accurately.

The corrected data MUST also be written on the site copy of the relevant form in the appropriate place in RED pen. The corrected data MUST be initialed and dated by the person resolving the query, as the example below:

**SURGICAL TECHNIQUES USED**

<table>
<thead>
<tr>
<th>Study Number</th>
<th>0 1 3 2</th>
</tr>
</thead>
</table>

**1. Actual date and time of start of Caesarean section (knife to skin):**

<table>
<thead>
<tr>
<th>Day</th>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**2. Type of anaesthesia (tick all that apply):**

- Local
- Spinal
- Epidural
- General

**3. Method of emptying bladder prior to surgery:**

- ‘in out’ catheterisation
- In-dwelling catheter for the duration

**10. Removal of placenta:**

- Controlled cord traction
- Manual removal
- Other

**11. Was the uterine cavity swabbed after delivery of the placenta?**

- Yes
- No

**Transfer of a woman recruited in your hospital to other hospitals (or wards)**

If a woman who has been recruited to CORONIS is to be transferred to another hospital or ward liaise closely with the hospital the woman is being transferred to and give the RTO the information listed below. It is very important to give the RTO this information so that follow-up at six weeks after discharge can be performed.

(i) your name and the hospital you are calling from
(ii) CORONIS Study Number
(iii) the woman’s name
(iv) the woman’s date of birth
(v) the name of hospital to which the woman is being transferred
(vi) the name of the receiving obstetrician / clinician

**12. Serious Adverse Event Reporting**

Serious Adverse Events should be reported to the Regional Trial Office within 48 hours. The RTO will then notify the International Co-ordinating Centre in Oxford who will report it to the relevant committees for review. As all of the surgical techniques being tested in this trial are used throughout the world there are no anticipated Serious Adverse Events as a unique consequence of participation in the trial.

We would, however, expect the following to be reported:

- Severe haemorrhage (requiring transfusion of six units or more of blood)
- Repeat laparotomy
- Hysterectomy
- Peritonitis
Deep venous thrombosis
Curettage of uterus
Internal iliac artery or other major artery ligation
Brace suture (e.g. B-Lynch suture)
Balloon tamponade
Uterine packing
Pulmonary embolism
Septicaemia
Any severe or unexpected morbidity should be reported.

13. Trial Monitoring
The RTO and the ICC will be monitoring the recruitment and data collection from participating sites continually.

From time to time your site may be visited by the RTO Study Co-ordinator, the Regional Co-ordinator or staff from the ICC. During these visits you will be asked to have available for review copies of all Consent Forms, Data Collection Booklet and the Allocation Envelope Box. The overall CORONIS system in your hospital will be reviewed.

These visits are to ensure that participating sites are adhering to the CORONIS protocol and procedures and to try to help with problems experienced by staff working on the CORONIS Trial. You will be given plenty of warning of the date of the proposed visit and will receive a feedback report following the visit.
**OBTAINING CONSENT**

Is woman undergoing delivery by lower segment caesarean through a transverse abdominal incision?

- Yes
  - Woman is **NOT** eligible for the CORONIS Trial

- No
  - Has the woman had more than one previous caesarean section?
    - Yes
      - Has the woman been recruited to the trial before?
        - No
          - Woman is **NOT** eligible for the CORONIS Trial

        - Yes
          - Woman is **NOT** eligible for the CORONIS Trial

    - No
      - Is there a clear indication for a particular surgical technique to be used?
        - Yes
          - Woman is **NOT** eligible for the CORONIS Trial

        - No
          - Collect an *Information for Women* leaflet and *Consent* form from CORONIS box

  - Talk to woman about the CORONIS trial (see *Obtaining Informed Consent* guide)

  - Has the woman agreed to participate in the CORONIS Trial?
    - No
      - Reassure woman this will not effect her treatment and treat as required

    - Yes
      - Woman signs *Consent* form (there are 3 copies)

      - Copy 1
        - Give the woman the top copy of the *Consent Form* and an ‘*Information for Women*’ leaflet

      - Copy 2
        - File the blue copy of the *Consent Form* in the Document Box

      - Copy 3
        - Fax or send the pink copy of the *Consent Form* to the Regional Trial Office
Complete the ‘At Study Entry’ section of the DCB BEFORE making randomisation call to the Regional Trial Office

Make the telephone call to the RTO to obtain allocation envelope number

Select the envelope which corresponds to the allocation number and remove the Allocation Form

Enter the details from the Allocation Form in the space provided on the ‘At Study Entry’ section of the DCB

Place ‘This woman is in the CORONIS Trial’ sticker on the outside of her notes

Is a particular suture material specified on the allocation?

Yes

Take 3 packs of allocated sutures from the CORONIS suture box

Place sutures in notes to go to theatre with the woman

No

Put Allocation Form and DCB in the woman’s notes to go to theatre

IT IS IMPORTANT to make the call as close to surgery time as possible
**AFTER SURGERY**

Remove the *Allocation Form* from woman’s notes and place in clear view of surgeon

Is a particular suture material specified in the allocation?

- **Yes**
  - Make suture available to surgeon
- **No**
  - Conduct surgery as specified on *Allocation Form*

Return *Allocation Form* to *DCB* in woman’s notes

**BEFORE SURGERY**

- Collect a *Medical card* and complete with woman’s name, date of birth, study number and appointment date
- Take *DCB* from woman’s notes
- Complete page 2 of the *DCB*
- Give woman her *Medical Card*
- Ensure surgeon completes pages 3-5 of the *DCB* and return to the woman’s notes

Complete all data forms using a black pen. All questions must be answered

Return unused sutures to the CORONIS suture box
**AT DISCHARGE FROM HOSPITAL**

Collect *DCB* from notes and complete pages 6-9

Send top copies of pages 2-9 to the RTO

**SIX WEEKS POST DISCHARGE & LONG-TERM FOLLOW-UP**

Where will the woman be seen at 6-weeks post-discharge?

- At the hospital? Yes
- At a local clinic? Yes
- At home? Yes
- By phone? Yes

Inform RTO that woman needs to be followed-up at home or by phone

RTO organise 6-week visit to the woman’s home / telephone call to complete Six Week Form

Organise 6-week follow-up before woman is discharged and put date on *Medical card*

Put *DCB* in woman’s notes

When pages 10-12 are complete, following the 6 week appointment, remove top copies from *DCB* and fax or send to the RTO

All data entered at the RTO and any queries clarified with recruiting centre / doctor

Organise regular contact with women to ensure long-term follow-up at 3 years post discharge

<table>
<thead>
<tr>
<th>Key</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Instruction</strong></td>
</tr>
<tr>
<td><strong>Question</strong></td>
</tr>
<tr>
<td><strong>Option or note</strong></td>
</tr>
</tbody>
</table>
CONTACT WITH WOMEN

To enable contact with women once they have been discharged from hospital, collect as much information as possible to ensure they can be contacted for the six week follow-up appointment or any further follow-up that might be conducted.

If at all possible the person making contact with the woman should be someone who has looked after her when she was in hospital.

Encourage women to contact the hospital or Regional Trial Office if they need to change their six week appointment. It is important to write a telephone number, either the hospital number or RTO number, on the woman’s Medical Card.

To assist in the long-term follow-up of ALL women a system of regular contact with the women during the three year period after discharge from hospital should be put in place. This system should use all available means e.g. phone, home visit or clinic attendance to ensure that the contact details are always correct and to record any serious events i.e. death of the woman.

DEFINITIONS OF TERMS IN DATA COLLECTION BOOKLET

Definitions for the section AFTER DELIVERY
Parity:
Include all births (livebirth or stillbirth) of viable fetus (estimated gestational age ≥24 weeks), including the baby delivered as part of the CORONIS Trial.

Best estimate of gestational age:
Please use the estimate of gestational age which is being used for clinical decision making. This may be based on the known last menstrual period date, an ultrasound scan or in the absence of this information, clinical examination of the abdomen.

Planned trial of scar:
This is women who have had a previous Caesarean section who are in labour as anticipated. If a woman with a previous Caesarean section presents in labour while waiting for her planned Caesarean section, tick the ‘No’ box.

Duration of Caesarean section procedure:
Length of operation in minutes from first skin incision until operative procedure is complete.

Definitions for the section POSTPARTUM STAY IN HOSPITAL
Operative procedures on wound:
This includes any procedures undertaken on the wound once the woman has left the operating theatre following her Caesarean section. It also includes further procedures under anaesthesia and removal of sutures without anaesthesia because of wound haematoma or infection. Operative procedures do NOT include use of pressure dressings. If uncertain, please tick ‘Yes’ and describe the procedure in the box provided.

Severe or unexpected maternal events:
Any severe or unexpected morbidity should be reported. This is most likely to include:
peritonitis, severe haemorrhage (requiring transfusion of six units or more of blood), repeat laparotomy, hysterectomy, deep venous thrombosis, curettage of uterus, internal iliac artery or other major artery ligation, brace suture (e.g. B-Lynch suture), balloon tamponade or uterine packing, pulmonary embolism and septicaemia. If uncertain, please tick ‘Yes’ and report the adverse event on the Serious Adverse Event Report Form which can be found in the CORONIS document box.
URGENT QUERIES

Contacting the International Co-ordinating Centre

1. **By telephone:**
   Phone **+44 1865 289750**, speak to a member of the Co-ordinating Centre staff or leave your name and number and someone will call you back.

2. **By text message:**
   Send a text message to **+44 07944876799**
   Give <YOUR NAME>, <YOUR TELEPHONE NUMBER>, <CORONIS STUDY>
   A member of the Co-ordinating Centre staff will call you back.

3. **By sending an Email:**
   Send an email to **coronis@npeu.ox.ac.uk**, include a telephone number so we can call you and an outline of the problem you have encountered.

4. **By fax:**
   Send a fax to **+44 1865 289740**, include a telephone number so we can call you and an outline of the problem you have encountered.
WHAT TO DO IF . . .

1. **A woman is randomised in error**
   If a woman is randomised in error, e.g. she has not given consent or has already delivered prior to the telephone call being made to the Regional Trial Office, send the completed *At Study Entry* page to the RTO immediately writing clearly at the bottom of the page the error that was made.

   You must collect all data for the woman and send it to the RTO. The data for any woman randomised in error will be excluded at the analysis stage but they will be counted in the overall number of women recruited.

   Try to avoid such situations by ensuring that consent is obtained, and the randomisation telephone call is made as close to the surgery time as possible.

2. **The telephone is out of order**
   If you are unable to telephone the Regional Trial Office (RTO) to obtain an envelope number because the telephone line is unavailable or out of order take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. It is very important you inform RTO staff so the numbered envelope that you have taken is not allocated to another woman.

3. **The RTO cannot connect to the internet**
   If you telephone the RTO and the internet connection is unavailable you will be asked to give the woman’s study entry details. The RTO staff will phone you back when the randomisation is complete with the number of the envelope to take for that woman. Complete the *At Study Entry* page with the number of the envelope you have been allocated and send it IMMEDIATELY to the RTO.

4. **The allocated envelope is missing**
   If you have been given an envelope number by the RTO staff and when you go to get it from the Allocation Envelope Box it is missing, you should take the LOWEST NUMBERED envelope (first envelope in the box). Complete the *At Study Entry* page with the number of the envelope you have taken and send it IMMEDIATELY to the RTO. Inform the RTO that you have been unable to use the allocated envelope so they can investigate where it may have gone and update the system accordingly.

5. **Wrong numbered envelope is taken**
   If you take the wrong numbered envelope by mistake you must record on the *At Study Entry* page the number of the envelope you have used in error, then:

   - Remove the numbered envelope that was allocated by the RTO staff from the envelope box.
   - Inform the RTO staff of the error. They will collect the unused envelope from you.
   - Complete the *At Study Entry* page with the number of the envelope you have actually used and send the page IMMEDIATELY to the RTO.
6. **Envelope is opened in error**
If an envelope is opened, either out of curiosity or because a member of staff was uncertain of the process, please call the RTO staff IMMEDIATELY and they will tell you how to proceed.

7. **The woman delivers vaginally after randomisation**
If the woman delivers vaginally after being allocated an envelope number, the woman is still in the study.

- Complete page 2 and pages 6-9 of the Data Collection Booklet.
- Put a line through pages 3-5.
- Follow-up the woman six weeks after discharge, then complete the final section of the Data Collection Booklet, pages 10-12.

If the woman is being followed-up at six weeks by the Regional Trial Office the follow-up personnel will complete the *Six Weeks After Discharge* form.

8. **Transverse incision is not possible**
If for any reason a decision has to be made to do a vertical incision after randomisation has taken place, please write the details leading to this decision on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to your RTO.

9. **Other information about the woman**
If you have information that you think may be relevant to the woman’s follow-up at six weeks or her long-term follow-up, i.e. tubal ligation during Caesarean section, please write it on the back page of the booklet, tear off the back page of the booklet and submit it with the DCB to the RTO.