Senate Community Affairs Committee

ANSWERS TO ESTIMATES QUESTIONS ON NOTICE

HEALTH AND AGEING PORTFOLIO

Budget Estimates 2012-2013, 30 & 31 May and 1 June 2012

Question: E12-075

OUTCOME: 1: Population Health

Topic: RU486

Type of Question: Hansard Page 50, 31 May 2012

Number of pages: 1

Senator: Senator Boswell

Question:

Have the treatment protocols of RU486 been submitted as part of each application for authorisation to supply RU486?

Please supply copies of each of those protocols.

Answer:

The protocols are developed by the institutions or organisations where the authorised prescribers practice and are approved by an ethics committee. These protocols are submitted and reviewed by the TGA and form part of the approval to supply mifepristone as an unapproved medicine.

There are currently 24 discrete protocols that have been submitted to the TGA by various institutions, organisations or individuals as part of an application for authorisation to prescribe mifepristone under subsection 19(5) of the *Therapeutic Goods Act 1989*.

Copies of the protocols, with identification of the prescribers and organisations where the prescribers work redacted for privacy reasons are attached.

Medical Protocols [redacted]

[redacted]

Early medical abortion using mifepristone and misoprostol

Rev	Date	Comments	By	Chk	App
1	May 2009	First version	[redacted]	[redacted]	May 2009
2	Aug 2009	Amendments	[redacted]	[redacted]	Aug 2009
3	Mar 2011	Scheduled review	[redacted]	[redacted]	June 2011
4	Dec 2011	Amendments following TGA request for opt-in monitoring	[redacted]		

Aim of this procedure

To outline the [redacted] process for medical abortion up to 9 weeks gestation.

When is this procedure used?

For all medical abortions up to 9 weeks gestation.

Who uses this procedure?

The Centre Manager is responsible for managing this policy.
All team members involved in the consultation and treatment process process.
Only appropriately trained providers endorsed by [redacted] can dispense mifepristone.

Using this procedure

Definition

The [redacted] is the brand name for the medication abortion process used in [redacted].

A medication abortion is an effective method for early abortion. It is the termination of early pregnancy resulting from abortion-inducing medications and without primary surgical intervention.

A mifepristone and misoprostol regimen is the preferred regimen at [redacted] in Australia.

[redacted]

NB. Medication abortions should only be undertaken in centres that have adequate access (either onsite or through arrangement with another provider) to medical facilities equipped to provide emergency treatment of haemorrhage, incomplete abortion and emergency resuscitation.

1. *Client Screening*

A [redacted] client can have a [redacted] at any time, provided she has made an informed voluntary choice, is no more than 9 weeks (63 days) gestational age and there are no medical contra-indications. She must meet the legal requirements for termination of pregnancy in the state where the service is provided.

There is the option for clients to have decision-making counselling.

1.1 Considerations

- Age
- Last normal menstrual period (LNMP)
- Menstrual history (regularity, flow)
- History of cramping, abdominal pain or vaginal bleeding since LMP (consider ectopic pregnancy and spontaneous abortion)
- Contraceptive use (correct or incorrect)
- Gravity and parity, including:
  - i) abortions, miscarriages
  - ii) history of ectopic pregnancy
  - iii) caesarean section, any obstetric complications
- Current symptoms of sexually transmitted infection (STI) or pelvic inflammatory disease (PID).
- Medical history (especially severe asthma)
- Blood pressure (BP)
  - refer if systolic BP is greater than 170, or diastolic BP is greater than 110
- Current medications
- Allergies

1.2 Contra-Indications to [redacted]

- Gestational age greater than 9 weeks (63 days). The client should be referred to have an [redacted] if up to 12 weeks. (Refer [redacted] *Procedure*)
- Known or suspected ectopic pregnancy – mifepristone and misoprostol are not effective treatments for ectopic pregnancy. (Refer *Early Pregnancy & Suspected Ectopic Pregnancy Policy*)
- Allergy to either mifepristone and/or misoprostol
- Adrenal failure or long-term corticosteroid therapy
- Haemorrhagic disorder or anticoagulant therapy
- IUD in situ – this must be removed prior to the MSMP taking place

- Presence of pelvic infection if severe (as indicated by abdominal/cervical motion tenderness, adnexal mass, mucupurulent discharge or high fever), this should be treated first. If mild, [redacted] can proceed once antibiotics have been commenced.

1.3 Special considerations

- Breast-feeding – there is a theoretical risk of diarrhoea in the breastfeeding infant. Defer breastfeeding for 6 hours following misoprostol.
- Severe anaemia
- Concurrent illness with significant diarrhoea
- Serious systemic illness – eg. liver disease, cardiac disease, renal disease, epilepsy, should be evaluated individually to determine the safest method of abortion.

1.4 Assessment of gestational age

All clients requesting termination of pregnancy must have an accurate assessment made of their gestational age.

An abdominal ultrasound should be performed to assess for the presence of an intra-uterine pregnancy and assess gestational age. Only if an intra-uterine gestation is not visible on abdominal ultrasound should a trans-vaginal ultrasound be considered. (Refer *Ultrasound Scanning Procedure*)

If an intra-uterine pregnancy cannot be confirmed, ectopic pregnancy must be excluded. (Refer *Early Pregnancy and Suspected Ectopic Policy*)

An ultrasound examination report from another provider confirming gestational age is acceptable. If there has been no history of pain or bleeding it is not necessary to repeat the ultrasound examination.

1.5 Laboratory Tests

a) Urine Pregnancy Test
A urine pregnancy test is not routinely performed. It is only required if an intra intra-uterine gestation is not visible on abdominal ultrasound, prior to proceeding to a trans-vaginal ultrasound.

b) Quantitative ßhCG Test
Serum levels should be measured where no intra-uterine gestation is confirmed but a urine pregnancy test is positive (refer *Early Pregnancy & Suspected Ectopic Pregnancy Policy*)

c) Rhesus (Rh) determination
All clients must have their Rh group determined and documented. The determination may be obtained on-site or by an external pathology provider. (Refer *Rhesus Determination and Administration of Anti-D Policy*)

d) Haemoglobin determination
Pre-operative haemoglobin determination is not routinely necessary in first trimester terminations. Severe anaemia can be detected while doing the physical examination and should be investigated and treated.

2. *Procedural Information and Informed Consent*

In order to make an informed choice, the client must be provided with information in language she can understand. Translated written information or a translating telephone service should be used when necessary

The client must understand the following eight points:

1) what a [redacted] is and how the mifepristone and misoprostol will be administered

2) that the client should be sure about having a [redacted] before proceeding but if she changes her mind she can decide against having the process at any time before it takes place

3) that there are certain risks as well as benefits involved in having a MSMP. These risks (below) must be explained in a way that the client can easily understand:
   - excessive bleeding
   - infection
   - retained pregnancy tissue
   - continuing pregnancy

4) that there are the following possible side-effects:
   - cramps and bleeding
   - nausea and vomiting
   - diarrhoea
   - fever / chills

5) that if the [redacted] fails to terminate the pregnancy, it is recommended that a surgical termination be performed as there may be birth defects associated with the medications used. There are reports of foetal malformations after the administration of misoprostol although the effect of mifepristone alone on a foetus is not known

6) the number of visits to the centre required, transport to and from the centre, and the telephone support available

7) that follow up contact is essential to ensure that the client does not have an infection, a continuing pregnancy or retained products of conception - vaginal bleeding is not proof of complete expulsion

8) that there is another alternative for first trimester abortion – the MSP (surgical aspiration abortion).

The client must be given the opportunity to ask for clarification of any of the process information as well as the opportunity to ask any questions and have them answered satisfactorily. It is also important to address any anxiety and questions that she may have about viewing the products of conception, as well as privacy and/or hygiene issues.

The reason for a client seeking a termination should be explored. The decision to go ahead with a [redacted] must be the voluntary decision of the client alone. This decision must not be made for the client by her husband, partner, family member, friend, service provider or anyone else.

The consent discussion and agreement to proceed must be carried out by the attending doctor. The client must sign the *Consent to the Use of Mifepristone and Misoprostol for Medical Abortion* and *Medical Abortion: Mifepristone & Misoprostol Risk Information Sheet* in the presence of the attending doctor.

Summary of comparisons between the [redacted] (mifepristone and misoprostol) and the [redacted]

[redacted] Medical Process	[redacted] Procedure
High success rate, but lower than a [redacted] (up to 98% - World Health organization, 2003)	High success rate (over 99%)
May be used in early pregnancy up to nine weeks since LMP	May be used in early pregnancy: up to 12 weeks since LMP
Usually avoids instrumentation	Instruments inserted into the uterus
Requires at least two centre visits	Can be completed in one centre visit
Medications cause a process similar to a miscarriage	A clinician performs the procedure
Abortion usually occurs within 24 hours of the second medication being taken	The procedure is completed in 5 - 10 minutes
The process will occur in your own home	Procedure performed at a [redacted]
Oral pain medication can be used	Local anaesthetic or intravenous sedation

4. *Contraception & sexual health screening*

Contraceptive options and appropriate sexual health screening must be offered to all clients undergoing a [redacted]

Screening for Chlamydia (PCR urine) is offered at the time of consultation. (Refer *Chlamydia Screening Policy*)

A contraceptive method may be started immediately after the [redacted]. Insertion of an IUD/IUS should be deferred until the 2 week check or at the next period. (Refer discharge instructions and *Initiation of Contraceptive Methods Policy*)

5. *The medical abortion*

5.1 Mifepristone

- blocks the action of progesterone and thereby:
  - stops the pregnancy growing and causes detachment
  - softens and dilates the cervix
  - makes the uterus more likely to contract
- rapidly absorbed orally in 15 minutes. If the client vomits more than 15 minutes after taking it, the dose does not need repeating
- supplied in 200milligram tablets, stored at room temperature

5.2 Misoprostol

- a prostaglandin licensed in Australia to prevent gastric ulceration caused by NSAIDs such as ibuprofen, naprosyn, and others
- makes the uterus contract, causing cramps and bleeding
- may cause short-lived nausea, vomiting, diarrhoea, fever or chills
- supplied in 200 microgram tablets, stored at room temperature

5.3 The [redacted] regimen

- Initial visit day 1: in the [redacted] the client takes **200mg** of mifepristone orally. The client is given 800 mcg of Misoprostol (4 tablets) to take home with clear instructions on their administration. (The dispensing of medications must be recorded in the Client Record and Mifepristone Register.)
- 24 - 48 hours after taking mifepristone the client takes **800mcgm** of misoprostol buccally at home, placing the 4 tablets between the cheek and gum for at least 30 minutes. Any undissolved tablet residue remaining after this time can then be swallowed.
- If no bleeding has occurred within 24 hours after the first dose of misoprostol, the client should return to the centre and be given a second dose of 800mcg misoprostol
- It is not necessary to inspect for products of conception
- The client may opt for a follow-up message from [redacted] 3 to 5 days following ingestion of mifepristone to remind them of symptoms that are of concern in relation to infection, incomplete abortion and therapeutic failure and of the support centre telephone number.
- Approximately 2 weeks after her initial visit, the client returns to the centre for an evaluation (see Follow-up Appointment below)
- Antibiotics are not given routinely
- For Rh negative women, Rh immune globulin (250IU) should be administered within 72 hours of the administration of mifepristone. (Refer *Rhesus Determination and Administration of Anti-D Policy*)

5.4 Bleeding and cramping

The onset of bleeding and cramping is usually within four hours of taking misoprostol; nearly all clients will have experienced the onset within 24 hours.

Sometimes bleeding can occur after taking mifepristone but before taking misoprostol. Misoprostol should still be taken as directed at the recommended time.

Bleeding occurs in almost all cases, however, this is not in any way proof of complete expulsion. A follow-up appointment is absolutely necessary to confirm that the pregnancy has been terminated.

Cramping can range from mild to severe.

Bleeding and cramping usually exceeds the typical levels of menstrual bleeding and cramping.

Bleeding and cramping should diminish once the pregnancy is expelled.

Significant cramping does not usually last longer than 24 hours.

Mild bleeding can continue for 30 days or more.

Problem bleeding:

- If a client saturates two (or more) sanitary pads per hour for two consecutive hours then this is designated 'problem bleeding'. As part of her discharge instructions the client **must be** given instructions about whom to contact if she experiences this type of bleeding.

Pain management:

- Counselling and reassurance are crucial to managing pain.
- Clients should be advised to rest, use hot packs on the abdomen and take pain relief medication as required.
- Analgesics such as paracetamol, ibuprofen, naprosyn and codeine may be beneficial taken shortly before the misoprostol and as required, at the recommended dose. NSAIDs can be taken with misoprostol.

5.5 Other side effects

These are generally short lived and may include:

- nausea
- vomiting
- diarrhoea
- fever and chills

6. *Discharge instructions*

The client must receive verbal and written discharge instructions in a language she can understand.

These instructions should cover the following:

- how and when the mifepristone and misoprostol are to be administered
- who to contact with any queries (including a 24 hour contact number)
- the normal range of symptoms and side-effects that a client can expect after taking these two forms of medication
- the use of pain relief medication
- the need for the client to have pelvic rest for one week (no sex or vaginal douching, no tampons, no bathing or swimming)
- the importance of keeping the follow up appointment in 2 weeks (please see below). Vaginal bleeding occurs in almost all cases and is not in any way proof of complete expulsion
- family planning methods should be started as soon as possible (as fertility can return in less than 2 weeks after a medical abortion). Oral contraceptives, vaginal rings, injectables and contraceptive implants can be commenced once bleeding has commenced following administration of misoprostol, or at the time of [redacted] if more practical. IUD/IUS may be inserted once abortion is confirmed to be complete or at the next period. All methods may be commenced at time of follow-up, if the possibility of repeat pregnancy can be confidently excluded (eg.

abstinence) and with appropriate advice given regarding the time to effectiveness. Refer *Initiation of Contraceptive Methods Policy*.

Warning signs and symptoms of possible complications:

The client should immediately return to the centre or seek immediate medical attention if she experiences:

- heavy vaginal bleeding (soaking two or more sanitary pads per hour for two consecutive hours or large fist-size clots)
- prolonged heavy bleeding or severe cramping
- severe cramping which is not relieved by pain relief medication
- feeling unwell, including weakness, nausea, vomiting or diarrhea with or without a fever~~, chills or malaise~~ lasting six or more hours or occurring more than 24 hours after misoprostol
- any abnormal vaginal discharge
- severe abdominal pain or nausea.

7. *Follow-up ~~appointment~~*

Follow-up message:

The client may opt for a follow-up message from [redacted] 3 to 5 days following ingestion of mifepristone to remind them of symptoms that are of concern in relation to infection, incomplete abortion and therapeutic failure and of the support centre telephone number.

Follow-up appointment:

The client must return for a follow-up appointment approximately two weeks after having a [redacted].

At this appointment the provider should take a history of events since the previous visit (see [redacted] *Client Feedback Survey* for much of this information).

Completion of the abortion process may be confirmed by a combination of:

- history of events
- signs and symptoms
- abdominal ultrasound examination
- urine pregnancy test (may be positive up to 30 days after a [redacted])
- falling serum ßhCG levels (if done)

The provider should assess for the presence of:

- a continuing pregnancy
- retained products of conception
- persistent heavy bleeding
- signs of infection

If the [redacted] is complete the provider should:

- answer any final questions the client may have
- review her contraceptive options

- provide information about additional health services as appropriate
- document completion of the process in the client record, noting any adverse events or complications

8. *Complications and their treatment*

8.1 Continuing pregnancy

Occurs in 1 – 2 % of all cases

Confirmed by an increase in gestational age, as measured on ultrasound examination, and in most cases a detectable foetal heartbeat. (A non-viable, non-progressing gestation is considered retained products - see below.)

Continuing pregnancy requires a [redacted] (aspiration abortion).

8.2 Retained products or "incomplete abortion"

Occurs in 1 – 2 % of all cases

If clinically suspected or evident on ultrasound only, without significant symptoms, such as heavy bleeding or cramping:

- give explanation that tissue may be expelled during subsequent vaginal bleeding or with next menstrual period OR
- give misoprostol, either 400mcg buccally or 600mcg orally as a single dose OR
- carry out a [redacted] (if it is the client's preference)

Persistent heavy bleeding or cramping requires a [redacted].

8.3 Excessive bleeding

The client should contact the centre or seek medical assessment if she saturates two (or more) sanitary pads per hour for two consecutive hours or experiences large, fist-size clots.

Excessive bleeding may require an [redacted] for clinically significant haemmorhage or if it is the client's preference.

A clinically significant haemorrhage is defined as:

- a drop in haemoglobin / haematocrit
- hypovolaemia
- othostatic hypotension

Ergometrine (0.2mg IM) can be administered up to three times, 5 – 10 minutes apart.

Haemorrhage requiring a transfusion occurs in 0.1 - 0.2% of all cases

8.4 Infection

Infections are rare in medical abortion (~0.3%).

Symptoms and signs of infection may include:

- persistent pelvic pain

- sustained fever over 38° C
- fever more than 24 hours after taking misoprostol
- atypical presentation can occur without fever, severe abdominal pain, or pelvic tenderness, but with significant leukocytosis, tachycardia, or haemoconcentration

For mild infections, oral antibiotics are prescribed:

Doxycycline 100mg bd for 10 days OR azithromycin 1g, repeated 1 week later

PLUS

Amoxicillin/clavulanate 875/125mg bd OR metronidazole 400mb bd for 10 days

If severe infection or sepsis is suspected, the client should be hospitalized for treatment.

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii* or other species e.g. Streptococcus) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. Most of these deaths occurred in women who used vaginally administered misoprostol. No causal relationship between mifepristone and misoprostol use and an increased risk of infection or death has been established.

8.5 Summary of situations necessitating surgical intervention

- continuing pregnancy
- incomplete abortion or retained products of conception associated with heavy bleeding or cramping
- orthostatic hypotension associated with haemorrhage or heavy bleeding
- anaemia, especially with on-going blood loss
- client unable to return to the centre or has no access to emergency services
- it is the client's preference

[redacted]

Documents Relating to this Procedure

Informed consent policy
Ultrasound Scanning procedure
Early Pregnancy and Suspected Ectopic policy
Rhesus Determination and Administration of Anti-D policy
Chlamydia Screening policy
Initiation of Contraceptive Methods Policy

Records Relating to this Procedure

[redacted] Admission Notes
Medical Abortion: Mifepristone & Misoprostol Information Sheet
Medical Abortion: Mifepristone & Misoprostol Risk Information Sheet
Consent to the Use of Mifepristone and Misoprostol for Medical Abortion
Medical Abortion Aftercare booklet
Mifepristone Drug Register

References to this Procedure

[redacted]

Termination of pregnancy - A resource for health professionals, RANZCOG, 2005
The Care of Women Requesting Induced Abortion - Evidence-based Clinical Guidelines Number 7, RCOG, 2011~~05~~
Frequently asked clinical questions about medical abortion, WHO, 2006

[redacted]

[redacted]

First Trimester Medical Interruption of Pregnancy Using Mifepristone and Misoprostol

This protocol outlines the process to be followed when using mifepristone and misoprostol for medical interruption of pregnancy at gestations <13 weeks.

Indications

Indications for mifepristone and misoprostol pregnancy interruption at <13 weeks gestation:

1. Intrauterine fetal demise in women in whom anaesthesia is potentially risky (eg. maternal cardiac or pulmonary disease) or surgical evacuation potentially difficult (eg. prior Ashermann's Syndrome, previous difficult or failed mechanical dilatation)
2. Severe fetal anomaly in which pathology assessment of the intact fetus is required
3. Severe maternal illness where continuation of the pregnancy would jeopardize the life or well-being of the mother

Medicolegal requirements

In [redacted] there is specific legislation for pregnancy termination[1] and at all times the requirements of this legislation are to be met.

It is a statutory requirement that all pregnancy terminations (non-fetal demise) are to be notified to the [redacted]

All women are to be counseled regarding the risks and potential complications of medical termination and written consent obtained prior to commencement of the procedure. This counseling information is to be documented in the hospital medical record chart.

Counselling and consent process

Appropriate counseling and legal requirements must be met in accordance with the [redacted].

Prior to hospital admission the following must occur:

1. Patient Information Booklet for medical first trimester termination be provided to the woman.
2. Completion of a consent form for medical termination of pregnancy and evacuation of retained placental tissue
    - Notation of the potential complications and side-effects

- Potential for surgical evacuation of retained placenta / fragments (approximately 5% of women will require this procedure)

Medical abortion procedure

- Medical termination of pregnancy will occur in two stages
    - Mifepristone 200mg orally (1 tablet) taken at home in the evening
    - Misoprostol vaginally as per the protocol below. Misoprostol is to be administered in hospital commencing in the morning 36 hours after the mifepristone was taken

- Mifepristone 200mg oral tablet is to be prescribed by a TGA-authorized prescriber and dispensed by the [redacted] The woman is to be instructed to take it by mouth in the evening 36 hours before her planned admission for misoprostol administration.

- Misoprostol is to be charted on admission as:-
    - Misoprostol 800ug (4 tablets) VAGINALLY followed 3 hours later if passage of the pregnancy has not occurred, by
    - Misoprostol 400ug (2 tablets) VAGINALLY every 3 hours to a maximum of two doses. These doses may be given ORALLY if there is vaginal bleeding.

The majority of women will expel the pregnancy within 4 hours of the vaginal misoprostol dose. If abortion has not occurred 4 hours after the final charted misoprostol dose the woman is reviewed by a doctor A speculum is passed and pregnancy tissue removed if it is visualized in the cervical canal. If no tissue is seen a pelvic ultrasound examination performed and a surgical evacuation proceeded to if the pregnancy is within the uterine cavity.

The median abortion interval from first misoprostol administration is 5 hours and the median number of doses of misoprostol is two.

94-95% of women will have a complete abortion with this protocol. 5-6% will require surgical evacuation of the uterus.

Following the passage of the pregnancy women are to be observed on the ward for 4 hours.

Following the administration of misoprostol, pulse, blood pressure, temperature and systemic symptoms are monitored hourly.

Potential risks with medical termination of pregnancy

Major complications from first trimester medical termination of pregnancy are rare but include:

- Haemorrhage requiring blood transfusion (0.2%)

- Infection

Lesser side-effects of the procedure used include:

- Prostaglandin side-effects: nausea, vomiting, diarrhea, fever
- Abdominal pain
- Bleeding

Contraindications to mifepristone/misoprostol medical termination

Known allergies to mifepristone or misoprostol
Severe asthma requiring corticosteroids
Suspected ectopic pregnancy
IUCD in situ (removed before treatment)
Chronic or acute adrenal or hepatic failure
Inherited porphyria
Bleeding disorders or concurrent anticoagulation therapy

Medical procedural requirements

- A Procedure Consent form must be signed by the woman and witnessed by the medical practitioner providing the counseling. This form must be completed prior to the mifepristone administration.
- FBC / group & hold are to be collected on admission.
- The following medications are also to be charted on admission:-
  - Misoprostol (see next section)
  - Diclofenac 50mg orally tds prn
  - Maxolon 10 mg IV / IM 6-hourly prn
  - Morphine 5 – 10 mg SC 3-hourly prn
  - Anti-D 625IU IM if the woman is Rhesus negative

Anxiolytic such as Lorazepam 1 – 2 mg orally 6-hourly prn.

August 2007

[redacted]

[redacted]

Midtrimester Medical Termination of Pregnancy Using Mifepristone and Misoprostol

This protocol outlines the process to be followed when using mifepristone and misoprostol for medical interruption of pregnancy.

When pregnancy interruption is required at gestations between 13 – 28 weeks, medical methods of evacuating the uterus are considered the optimal in terms of maternal safety[1]. Surgical evacuation of the uterus may be employed but requires specific training and an ongoing case-load to maintain this skill, a situation which is not available at [redacted]. In addition, when examination of the fetus is indicated for medical diagnosis or the parents wish to view their fetus, medical termination is indicated.

There may be specific circumstances where a medical termination of pregnancy in the first trimester is the safest option for the health of the mother (eg. severe maternal cardiovascular disease).

Indications

Indications for mifepristone and misoprostol pregnancy interruption (13-28 weeks gestation):

1. Intrauterine fetal demise
2. Severe fetal anomaly
3. Severe maternal illness where continuation of the pregnancy would jeopardize the life or well-being of the mother
4. Previable preterm prelabour rupture of membranes with oligohydramnios

Medicolegal requirements

In [redacted] there is specific legislation for pregnancy termination[2] and at all times the requirements of this legislation are to be met.

At gestations beyond 20 weeks, pregnancy termination (regardless of indication when the fetus is alive) specifically involves permission from the [redacted]. No termination procedure will be commenced at gestations greater than 20 weeks until [redacted] permission has been obtained.

It is a statutory requirement that all pregnancy terminations (non-fetal demise) are to be notified to the [redacted]

All women are to be counselled regarding the risks and potential complications of medical termination and written consent obtained prior to commencement of the procedure. This counselling information is to be documented in the hospital medical record chart.

Particular circumstances requiring individualisation of care

1. Prior uterine surgery

The presence of a uterine scar should be noted. Whilst the risk of uterine rupture in women with prior uterine surgery is low (<1%) during termination procedures using prostaglandins alone or in combination with mifepristone, it is a potential adverse event and must be discussed with the woman. Clear documentation of this discussion must be made in the medical record chart. It must also be recognized that uterine rupture is a complication of any method of mid-trimester pregnancy termination, regardless of the presence of absence of prior uterine surgery.
On occasions, medical termination methods may not be appropriate for women with prior uterine surgery and treatment options must be individualized.

2. Third trimester

Misoprostol should not be used in the third trimester in the doses employed in the second trimester. At present, consideration for the use of mifepristone and a low dose misoprostol regimen could only be made in the context of a scientific trial, appropriately reviewed and approved by the regulatory authorities at [redacted]
In second trimester pregnancies with a fetal size greater than 28-30 weeks, pregnancy interruption options should be individualized.

Counselling and consent process

Appropriate counselling and legal requirements must be met in accordance with the [redacted]

Prior to hospital admission the following must occur:

1. The Patient Information Booklet for medical midtrimester termination is discussed and given to the woman.
2. Completion of a consent form for medical termination of pregnancy and evacuation of retained placental tissue
   - Notation of the potential complications and side-effects
   - Potential for surgical evacuation of retained placenta or fragments (approximately 10-20% of women will require this procedure)
3. Inform the woman that the termination procedure will involve the use of oral mifepristone, a progesterone receptor blocker prior to the vaginal administration of the prostaglandin misoprostol. There have been many scientific studies clearly demonstrating the efficacy of this

sequential medication regimen with the primary medical benefits being a reduction in duration of hospital stay, a reduction in placental retention rates and a reduction in procedure-related pain compared with misoprostol administration alone.

Mifepristone is not generally available in Australia for pregnancy interruption although it is licensed for this purpose in many countries (eg United Kingdom, France, USA, New Zealand). Multiple scientific publications attest to the safety and efficacy of mifepristone when used to prime the uterine response to prostaglandins such as misoprostol. The Therapeutic Goods Administration (TGA) and the [redacted] have given approval for some medical practitioners at [redacted] to prescribe mifepristone for this purpose.

Misoprostol is the principal prostaglandin used at [redacted] to induce medical termination of pregnancy in the mid-trimester of pregnancy. In Australia misoprostol is licensed for the treatment of stomach ulceration but not for use in pregnancy. As with mifepristone, there are many scientific studies, including several clinical trials conducted at [redacted] which clearly demonstrate the effectiveness and satisfactory safety profile of misoprostol compared with the licensed product gemeprost (Cervagem). Misoprostol has advantages over gemeprost in terms of storage, cost and routes of administration. Misoprostol is used "off label" in obstetrics and gynaecology as the current sole manufacturer does not wish to have it licensed for pregnancy use. The "off-label" use of medication is not uncommon, particularly in obstetrics and paediatric medicine. As the efficacy and safety of misoprostol is medically accepted, the [redacted] and [redacted] gave approval for the "off-label" use of misoprostol in pregnant women.

Potential risks with medical termination of pregnancy

Very uncommonly serious complications may occur during midtrimester pregnancy termination. These complications are not specific to the process but rather are inherent complications of labour. In Australia, maternal death during pregnancy or labour is rare, with an incidence of approximately 1 per 10,000 women.

The most serious complications of labour and birth include:

- Haemorrhage requiring blood transfusion (1-2%)
- Unplanned major abdominal surgery because of heavy bleeding or rupture of the uterus or problems with the placenta (0.5%)
- Unplanned emergency hysterectomy (0.2%)

There have been a handful of reports internationally of a fatal toxic shock type infection with *Clostridium sordellii* associated with mifepristone use (1/100,000 risk)

Minor side-effects of the medications used include:

- Mifepristone
  - Nausea and vomiting 15 – 20%
  - Headache 15 - 20%
  - Occasional pelvic cramping before admission
- Misoprostol
  - Fever > 37.5 degrees 50%
  - Nausea and vomiting 25-50%
  - Diarrhoea 5%

The incidence of misoprostol side effects is related to the number of doses given. When pre-treatment with mifepristone is utilised, significantly fewer doses of misoprostol are needed than when used as a sole abortifacient agent.

Termination procedure

- All midtrimester terminations of pregnancy must be overseen by a consultant
- Only in exceptional circumstances should women undergo a midtrimester termination of pregnancy and surgical sterilisation during the same admission. The responsible consultant must personally review such women.
- Medical termination of pregnancy will occur in two stages
  - Mifepristone 200mg orally (1 tablet) taken at home in the evening
  - Misoprostol as per the protocol below. Misoprostol is to be administered in hospital commencing in the morning 36 hours after the mifepristone was taken
- Mifepristone 200mg oral tablet is to be prescribed by a TGA-authorised prescriber and dispensed by the [redacted]. The woman is to be instructed to take it by mouth in the evening 36 hours before her planned admission for misoprostol administration.
  If the gestation is 13-19 weeks the woman is admitted to Ward 6 (admission timing is prebooked with the nurse manager on page [redacted] prior any mifepristone prescription).
- If the gestation is >20 weeks gestation the woman is admitted to the Labour Ward [redacted] permission must be obtained prior to booking). The timing must be arranged with the Labour Ward prior to any mifepristone prescription (telephone [redacted]).
- A Procedure Consent form must be signed by the woman and witnessed by the medical practitioner providing the counselling. This form must be completed prior to the mifepristone administration.
- FBC / group & hold are to be collected on admission.
- The following medications are also to be charted on admission:-
  - Misoprostol (see next section)
  - Diclofenac 50mg orally tds prn
  - Maxolon 10 mg IV / IM 6-hourly prn
  - Morphine 5 – 10 mg SC 3-hourly prn
  - Cabergoline 1 mg stat orally is to be offered after deliveries > 18 weeks gestation for lactation suppression.

- Anti-D 625IU IM if the woman is Rhesus negative
- Anxiolytic such as Lorazepam 1 – 2 mg orally 6-hourly prn

- Misoprostol is to be charted on admission as:-
  - Misoprostol 800ug (4 tablets) VAGINALLY followed 3 hours later by
  - Misoprostol 400ug* (2 tablets) ORALLY or VAGINALLY every 3 hours to a maximum of four oral doses.
    - This regimen is only for pregnancies **<22 weeks gestation.** Gestations >22 weeks gestation the misoprostol loading dose is omitted.
    - *Women with a dead fetus > 20 weeks gestation in the presence of a uterine scar should receive 200ug (1 tablet) rather than 400ug.
  - 97% of women will deliver with this regimen, most within 15 hours. Undelivered women must be reviewed by a registrar or consultant after which the following will generally be prescribed:
    - Mifepristone 200mg orally to be given at midnight, followed the next morning by
    - Misoprostol 800ug (4 tablets) VAGINALLY followed 3 hours later by
    - Misoprostol 400ug* (2 tablets) ORALLY or VAGINALLY every 3 hours to a maximum of five total vaginal doses including the 800ug dose. *200 ug for fetal demise with a prior uterine scar.
  - Women still undelivered after this second course (about 0.3%) must be reviewed by a consultant. Subsequent management options include:
    - Repeating above regimen
    - Extra-amniotic PGF2α
    - Amniotomy and syntocinon infusion
    - Surgical evacuation of the uterus

The woman is to remain on the bed for 60 minutes after any vaginal dose of misoprostol to optimize absorption.

- Dosing can continue after the membranes rupture if delivery is not imminent.
- Observations to be performed:-
  - BP, pulse and temperature on admission and thereafter fourth-hourly unless required more frequently by the clinical situation.
  - A fluid-balance chart is usually not required. However, one should be used in women who are at risk of dehydration such as those:
    - having significant vomiting and diarrhoea
    - who have not delivered in the first 24 hours and whose oral intake is limited
    - having extra-amniotic PGF2α
- Diet:-
  - Clear fluids after onset of contractions (full diet until then)
  - Fast once membranes have ruptured and remain fasting until placenta delivered and declared complete

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Placental management

- Oxytocin 10 IU is administered intramuscularly after expulsion fo the fetus.
- Placental retention will occur in about 10-20% of women (under 20 weeks it will be higher) and women should always be consented for possible operative removal when being consented for pregnancy termination.
- If the placenta is not expelled within 60 minutes of delivery of the fetus (earlier if bleeding is excessive), assisted removal is indicated. Placental removal is generally conducted in the operating room.
- A broad-spectrum intravenous antibiotic should be administered if manual removal of placenta is undertaken.

Lactation Suppression

- Cabergoline 1mg as a single oral dose, taken with food, is routinely offered for lactation suppression in gestations terminated at 18 weeks or greater.

Paperwork and cremation/burial requirements

- These must be attended as per existing Procedures for the management of stillbirths, neonatal deaths and fetal anomalies.
- The Notification of Termination (Form 1) must be completed and forwarded to the [redacted] following any pregnancy termination.

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Attachment 2:

Mifepristone and misoprostol for medical abortion

Indications and regimens for prescription and use of the unapproved product mifepristone, 200mg tablets at the [redacted]

July 2009

Indications for use of mifepristone
Termination of pregnancy where medical abortion is assessed clinically as the most appropriate method for the woman, including when surgical abortion is not available. This would include:

- women who have had a failed attempt at surgical abortion
- women for whom surgical abortion carries higher than usual risk or likelihood of failure or is contraindicated
- women where on balance medical abortion is more appropriate than surgical abortion for clinical reasons including anaesthetic risk or very early pregnancy
- women having termination of pregnancy at an advanced gestation, when the Women's does not offer surgical abortion and the alternative is medical management with misoprostol alone (routine after 18 weeks and some cases at 14-18 weeks)
- fetal death in utero, including early miscarriage
- women with a strong preference for medical abortion over surgical abortion

Gestational considerations
After 28 weeks gestation mifepristone with misoprostol would only be used in the presence of fetal death in utero.

Site of prescription and use
Care will be provided at [redacted]. Specifically the mifepristone and misoprostol will be administered under direct supervision at [redacted]. It is anticipated that the vast majority of women treated will proceed to complete the abortion on the premises. In exceptional cases, if abortion does not occur or is not complete within a few hours of misoprostol, outpatient follow up will be arranged, or transfer to another institution, staffed and equipped to conduct pregnancy termination.

Regimens at [redacted]
[redacted] uses the regimens recommended by the Royal College of Obstetricians and Gynaecologists (RCOG), as also reported in several large case series.

Up to 63 days gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- A further dose of 400 µg misoprostol administered orally or vaginally if products of conception not passed within 4-6 hours.

63-91 days gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- Further doses of 400 µg misoprostol administered orally or vaginally at 3 hourly intervals up to a maximum of five doses if products of conception not passed.

13-24 weeks gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- Further doses of 400 µg misoprostol administered orally at 3 hourly intervals up to a maximum of four doses if products of conception not passed.
- Consideration of a repeat course of treatment if unsuccessful.

After 24 weeks gestation:

- As for 13-24 weeks gestation, but dosage of misoprostol may be reduced and intervals increased as judged appropriate by the clinician.

Since the previous application there has been a growing body of evidence supporting the efficacy of sublingual administration of misoprostol as an alternative route to oral or vaginal administration.

Potential variations may be made according to clinical judgment in individual cases, or if new evidence supports a change:

- Variation of the interval between mifepristone and misoprostol (evidence supports this being 1-3 days)
- Variation of the misoprostol regimen, including route of administration, specifically sublingual administration
- Substitution of gemeprost for misoprostol in accordance with RCOG guidelines and approved UK regimens

[redacted] has procedures in place to ensure that informed consent is obtained and to support delivery of care, provision of information and appropriate follow up.

Referrals for medical abortion

[redacted] still does not propose to seek or accept referrals solely for the purpose of access to mifepristone. However [redacted] already accepts patients at higher than usual risk or who have had a failed surgical abortion elsewhere, as a routine part of its role as a tertiary referral centre.

Failed medical abortion

As with failed surgical abortion, if medical abortion fails, there needs to be clinical discussion about how best to proceed to complete the termination. Options might include a further course of mifepristone and misoprostol, surgical abortion, intrauterine injection with a range of agents or even hysterotomy, depending on the particular clinical circumstances.

Monitoring and reporting

Audit will be undertaken of all cases where treatment with mifepristone is used, including recording of dosage regimens, outcomes, adverse events and follow up. Reports will be made at least annually to the Hospital's Quality and Safety Committee and to [redacted] Suspected adverse events will be reported to the TGA, the sponsor and the [redacted]

Revisions to practice, information and consent forms

New evidence may lead to changes in treatment regimens. Any necessary changes will be reviewed and approved prospectively by the Chief Medical Adviser, [redacted] and notified to the [redacted]

taken to complete abortion and pain experienced by women undergoing the procedure (Rodger & Baird 1990).

Mifepristone is also indicated for adjunctive use in first and second trimester surgical abortion. While surgical abortion procedures present less risk to the pregnant woman than continuing a pregnancy to term, there are some adverse outcomes. Surgeons conducting such procedures are engaged in a continuing process of quality improvement as they seek to reduce the frequency of adverse outcomes. Mifepristone offers the prospect of reducing complication rates in surgical abortion by reducing the requirement for mechanical dilation of the cervix and the time taken to complete the surgical procedure.

The product - active ingredient

Mifepristone is a competitive antagonist of progesterone which binds to progesterone receptors and glucocorticoid receptors (Ashok & Wagaarachchi 2002). By preventing the effects of progesterone in the uterus, it interferes with implantation and placental development, resulting in foetal inviability. The mechanism of action is essentially to mimic the syndrome of luteal insufficiency, in which there is insufficient secretion of progesterone from the corpus luteum. This syndrome is a common cause of early spontaneous abortion. Inhibition of progestogenic effects is also a very logical approach to post-coital contraception.

Mifepristone was first tested for induction of abortion in 1982 and licensed for use in inducing early medical abortion (in combination with a prostaglandin analogue) in France in 1988, in the United Kingdom in 1991 and in the USA in 2000. Millions of women have now been treated with mifepristone worldwide.

Trade name, dose form, supplier

Cipla India 200mg mifepristone tablets for oral administration.
Danco USA "Mifeprex" 200mg mifepristone tablets for oral administration.
Exelgyn France (per IDIS UK)"Mifegyne" 200mg mifepristone tablets for oral administration.

Indication: second trimester medical abortion

Clinical justification

In some circumstances, pregnancy may constitue both a life threatening and a serious condition, therefore treatments which reduce the risk to the pregnant woman by terminating a pregnancy meet the requirements of Regulation 12B(2) of the Therapeutic Goods Act.

Justification for use of mifepristone in preference to other approved treatments

Over 100 second trimester medical terminations of pregnancy are conducted each year at [redacted]. The currently available methods for termination of pregnancy in the second trimester are surgical (dilation and evacuation) or medical (misoprostol only induction).

Surgery is offered for gestations up to 16 weeks and entails pretreatment with misoprotol followed by dilation of the cervix and evacuation of the uterine contents.

A medical method is used in the management of pregnancies over 16 weeks gestation with admission and induction of labour using misoprostol.

Both of these methods entail "off label" use of misoprostol, which is registered on the Australian Register of Therapeutic Goods for other indications. While the current medical and surgical methods for second trimester abortion pose less risk to some pregnant woman than continuing her pregnancy to term, rare but serious adverse outcomes are associated with these procedures and attention is directed to reducing risks such as haemorrhage requiring transfusion (for medical procedures) or uterine artery laceration requiring hysterectomy (for surgical procedures). The addition of mifepristone offers the prospect of reducing risks to women undertaking second trimester abortion.

Jurisdictions in which Mifepristone is approved for this indication

United Kingdom

Efficacy and safety of mifepristone in second trimester abortion

Both medical and surgical approaches are highly effective in terminating second trimester pregnancies. Fewer abortions are carried out in the second trimester than in the first trimester and consequently trials and case series involve smaller numbers than those reporting on the efficacy and safety of first trimester abortion methods.

The effectiveness of second medical trimester abortion procedures is high. Mazouni et al (2006) reported a failure rate of 1/202 (0.5%) following second trimester medical abortions using misoprostol only between 15 and 24 weeks. In Australia Dickenson (1998) reported a series of 1001 second trimester medical abortions (using misoprostol only) in which 39 (3.9%) did not deliver within 48 hours. A recent Danish series of 127 abortions conducted at 13 to 24 weeks reported that abortion took place within 24 hours in 98% (Nilas et al 2007). For surgical approaches effectiveness approaches 100% and abortion failure rates are not reported in the second trimester series.

Safety of second trimester surgical abortion in comparison to medical abortion

In series of 1064 surgical abortions using osmotic dilators and surgical evacuation at 14 to 22 weeks gestation has Schnieder, Bukovsky & Caspi (1994) reported that 8/1064 had disseminated intravascular coagulation and 2/1064 significant haemorrhage. In a series of 1867 surgical abortions at 13 to 20 weeks conducted in South Australia, Pridmore and Chambers (1999) 6 uterine perforations were observed. Surgical injuries are avoided by medical termination procedures. There is a small risk of uterine injury arising from surgical approaches to second trimester abortion and a similarly small risk of uterine rupture arising from medical approaches (see below).

Safety of second trimester medical abortion with mifepristone and misoprostol in comparison to current practice using misoprostol only

The main differences between second trimester medical abortion using misoprostol alone and using mifepristone pre treatment prior to misoprostol are

1) a reduction in the time elapsing between induction to abortion, with consequent reductions in pain and analgesic requirements.
2) A reduction in retained placenta, often associated with haemorrhage and need for transfusion, and requiring surgery to evacuate the uterus.
3) A potential reduction in the risk of uterine rupture associated with the use of misoprostol in women with previous uterine scar, through a reduction in the amount of misprostal required to effect delivery and time to delivery.

Placental retention and transfusion

Daskalakis (2005) reported other serious outcomes after misoprostol-only abortions, such as significant haemorrhage in 0.9% and retained placenta (requiring surgical intervention) in 52.5%. In Australia in a series of 1001 consecutive second trimester medical abortions conducted in Western Australia using misoprostol only, 315/1001 (31%) had retained placental tissue and 21/1001 (2%) required transfusion (Dickenson 2007).

Induction to delivery time

Rodger & Baird (1990) demonstrated that pretreatment with mifepristone reduces interval between prostaglandin administration and expulsion in second trimester abortion nearly two decades ago. In their randomised trial involving 100 women pre-treatment resulted in a median induction to abortion interval of 6.8 hours which was significantly less than 15.8 hours in the control group (misoprostol only). Since then, the adoption of mifepristone pre treatment prior to misoprostol induction of second trimester abortion has produced such a marked drop in the length of time required for most medical abortions

that it has become possible to manage many second trimester abortions as day cases in countries where it is available (Lalitkumar 2007:46).

Ashok & Kidd (2004) administered the same combination of mifepristone and misoprostol that is proposed for use in Brisbane to 500 women with gestations of 13 to 21 weeks producing a median time from induction to abortion of 6.5 hours.

In Australia Dickenson (1998), in a comparison of gemeprost and misoprostol used in induction of second trimester abortions at 17 to 22 weeks, found that the average induction to delivery time was 16.9 hours amongst the 53 given misoprostol only. In contrast Hamoda et al (2005a) reported median induction to delivery times of less than 8 hours in each of three arms of a trial involving 76 women given three different misoprostol regimens following 200mg of mifepristone. The difference in the time taken to abort is clearly illustrated by Lalitkumar et al(2006:table 42-44) in their review of 21 trials of second trimester medical abortion regimes where all of the misoprostol only regimens resulted in longer procedures than any of those involving pre treatment with mifepristone.

Pain

Medical abortion in the second trimester commonly involves pain. Reporting on a series of 99 patients having induction of labour using mifepristone and misoprostol for either foetal death or as an abortion procedure, Verhulsdonk (2007) found that 28% required epidural anaesthesia and a further 24% were given intramuscular pethidine during the procedure. In the original study which demonstrated shorter induction to delivery time when mifepristone was used (Rodger & Baird 1990) there were also significantly fewer analgestic injections given to 49 women in the mifepristone group (ave 1.1) than in the group of 50 using misoprostol only for induction of second trimester abortion (ave 1.5, $P<0.05$).

Uterine rupture

There are case reports of uterine rupture during second trimester abortion with misoprostol (Nayki et al 2005). One such event was seen in a series of 324 second trimester abortions conducted using misoprostol between 17 and 24 weeks gestation by Daskalakis et al (2005) and one was reported amongst 297 women having misoprostol only second trimester abortions reported by Autry et al (2002), however none were observed in a recent series of 1001 second trimester abortions using misoprostol only in Western Australia (Dickinson 2007).

Other side effects of treatment

In their series of 53 second trimester abortions with misoprostol only, Dickenson, Godfrey & Evans (1998) observed nausea in 18/53 (34%), diarrhoea in 1/53 (2%), fever

over 37.5 C in 18/53 (34%)and a pain score greater than 5 in 24/53. All of these side effects are associated with misoprostol and are not expected to diminish with a mifepristone and misoprostol regimen except to the extent that shorter induction to delivery times will result in fewer doses of misoprostol being required. One trial comparing different routs of administration of misoprostol following mifepristone found fewer gastrointestinal side effects amongst 20 women given the misoprostol vaginally than amongst the 29 who were given oral misoprostol doses (Fairley et al 2004).

In summary, the current practice of using misoprostol only for medical abortion in the second trimester infrequently results in uterine rupture. Transfusion is required following 1 – 2% of procedures and the rate at which surgery is required to remove placental tissue varies from less than 10% to over 50%. Mifepristone has the advantage of reducing both the duration of the process and the dose of misoprostol required, the rate of placental retention and need for associated surgery.

Administration regime; Proposed protocol for second trimester medical abortion

Following appropriate counselling, and where medical abortion can be offered, those women with pregnancies over 13 weeks gestation will have mifepristone 200mg oral administered as outpatients. Women will be admitted 24-36 hours later for induction of labour using 400 micrograms of misoprostol po and 400 micrograms of misoprostol pv and further doses of 400 micrograms every 6 hours. Immediate access to surgical facilities are available if needed.

Monitoring

Every woman choosing medical abortion with mifepristone will be invited to consent to a review of her medical records within 12 months following treatment. A review of the paper medical record will be undertaken to allow an audit of any adverse outcomes. The majority of women are reviewed 6 weeks following the procedure and follow up arranged if there are any issues in regards to persitant bleeding or infection. Women not followed up in the treating hospital will be telephoned by the nursing case manager to identify and record any post-treatment adverse events (with consent).

Indication: Cervical priming prior to surgical abortion in the first and second trimesters

Safety and efficacy of cervical priming with mifepristone

The rate at which serious adverse events occur in surgical second trimester abortions is well documented. Most serious outcomes are consequent to trauma caused by instrumentation. Uterine perforation is diagnosed following fewer than1:1000 abortions. These injuries may result in serious haemorrhage and may require emergency hysterectomy when they occur in the second trimester. In a South Australian series of

13907 surgical abortions the perforation rate was 0.9%. This rate fell to 0.5% following modification of cervical priming regimens with reduction in mechanical dilation of the cervix at surgery (Mulligan 2006).

Research concerning the effectiveness of cervical priming with mifepristone prior to surgery has studied proxy measures of surgical trauma; the baseline cervical dilation achieved by priming (obviating the need for surgical instrumentation to achieve this dilation) and the force required of the surgeon to pass further dilators through the cervical canal (equating greater force to greater risk of traumatic injury). Ashok, Wagaarachchi et al (2002:9) have reviewed 4 clinical trials involving 340 women who received mifepristone, misoprostol or gemeprost prior to surgery. The baseline cervical dilation achieved was greater with mifepristone than gemeprost, particularly following a delay of 48 hours from treatment, and the force required for further dilation was less following priming with mifepristone priming in comparison to either misoprostol or gemeprost.

Carbonell et al (2007) have reported on a randomised trial which compared misoprostol only (sublingual, vaginal or oral routes) with mifepristone plus misoprostol (sublingual or vaginal) prior to 900 surgical abortion procedures conducted at 12 to 20 weeks. The average cervical dilation achieved with mifepristone priming was 12.5mm +/-2.8mm (95%CI 12.3 – 12.8) while this was significantly less in the misoprostol only groups averaging 8.5mm +/- 3.2mm (95%CI 8.2 – 8.8). The average length of the procedure (a proxy measure of surgical difficulty) was less in the mifepristone treatment groups although this difference did not reach statistical significance.

Administration route dosage duration

Following appropriate counselling, medical and anaesthetic assessment where surgical abortion is offered mifepristone 200mg oral will be administered 12-24 hours prior to admission for surgery. Pre operative cervical ripening will also be undertaken using misoprostol 400 micrograms po.

Monitoring

Every woman offered cervical priming with mifepristone prior to surgical abortion will also be invited to consent to a review of her medical records within 12 months following treatment. Where any encounter diagnosis suggests a post treatment complication, a review of the paper medical record will be undertaken to allow an audit of any adverse outcomes treated in public hospitals.

Indication; Medical termination of pregnancy in the first trimester

Clinical justification

In some women pregnancies are both serious and potentially life threatening, and therefore treatments which reduce the risk to the pregnant woman by terminating a pregnancy meet the requirements of Regulation 12B(2) of the Therapeutic Goods Act Regulations.

Justification for use of Mifepristone in preference to other approved treatments

Internationally, there are two major approaches to first trimester abortion: surgical and medical. Although both of these approaches are currently used in Australia, surgical methods are by far the most commonly employed because of the lack of a key component (mifepristone) of the most appropriate drug regimen for induction of first trimester abortion (mifepristone and misoprostol).

The most commonly available method for termination of pregnancy in Australia in the first trimester is surgical dilation of the cervix followed by suction evacuation of the uterine contents. Cervical priming with the prostaglandin analogue misoprostol (200 to 800 micrograms po), is often undertaken prior to surgery.

Women present a myriad of differing clinical circumstances which may prompt a treating practitioner to recommend one or the other method as the safer or more acceptable option in the individual circumstances.

A Cochrane systematic review of trials comparing medical and surgical abortion methods has concluded that there is little difference in their efficacy (Say 2002:1). No significant difference in the rates of treatment failure (ongoing pregnancy) following treatment with medical and surgical methods was detected in the meta-analysis of trials included in this systematic review. Most of the trials involved small numbers of women, and since ongoing pregnancy is an infrequent outcome it cannot be meaningfully quantified by small trials.

A comparison can be made between the reported rates in case series. In one large series of surgical abortion, that included 33,090 procedures a rate of unrecognised failed abortion of 2.3 per 1000 was reported in an early series (Kaunitz et al 1985). A similar rate of failure (32/ 23,000 or 1.8 per 1000) was observed in Turkey (Zorlu et al 1996). In comparison, a series of 95,163 medical abortions conducted in the United States using mifepristone and misoprostol reported 330 continuing pregnancies or 3.5 per 1000 (Henderson et al 2005:176) and in a report from the United Kingdom on 4123 medical abortions using mifepristone and misoprostol there were 13 ongoing pregnancies, or 3 per

1000 (Ashok, Kidd et al 2002). These were not comparative trials, however observed rates of ongoing pregnancy were similarly low following medical and surgical abortion in these large series.

A more recent Cochrane systematic review of medical methods for first trimester abortion (Kulier et al 2004) reviewed 39 trials comparing different regimens and concluded that a combination of mifepristone with a prostaglandin (the regimen proposed for South Australia) was more effective than any single agent in terms of the induction of complete abortion, but does not report on the rate of continuing pregnancy.

Provider preference

The treating medical practitioner may recommend medical methods for women who have higher anaesthetic or surgical risk factors especially where surgery would be more difficult due to unusual anatomy. For example, Zorlu et al (1996) identified 9 patients with unusual uterine anatomy amongst 33 cases where an attempt at surgical abortion in the first trimester had failed. Both providers and patients would benefit from the availability of an alternative, non surgical method.

Jurisdictions in which Mifepristone is approved for this indication

France 1988, China 1988, United Kingdom 1991, Sweden 1992, USA 2000

Administration regime

It is proposed to continue established pre procedure protocols for the management of women seeking first trimester pregnancy termination. Two medical practioners assess the patient and confirm that termination is lawful under the [redacted] Criminal Code and [redacted] Policy. Where medical abortion can be offered and is the safer or preferred option, the proposed procedure for mifepristone based abortion would vary depending on gestation.

Medical abortion up to 63 days from last menstruation

Where medical abortion can be offered, those women with pregnancies of 9 completed weeks gestation or less who choose this option would have mifepristone 200mg oral and misoprostol 800 micrograms per vagina administered in the clinic and be discharged to home with a further 400micrograms of misoprostol to be taken orally or vaginally next day if the products of conception do not pass (a highly effective regimen researched by Ashok, Kidd et al 2002 and supported by Kulier 2004). In addition women would receive written and verbal instructions concerning when and how to access further medical

assistance after hours, what pain relief to take and routine follow up instructions to return to the clinic in 7 days time for ultrasound or quantitative beta HCG testing to confirm completed abortion. Those with a continuing pregnancy at follow up (expected rate 3-4:1000) will be offered a choice of repeat medical treatment or a surgical procedure. Those who have retained products of conception visible on ultrasound at follow up (expected rate 1 or 2:100) will be offered misoprostol 200 or 400 micrograms tds for 2 days as a first line treatment followed by surgical evacuation if the retained products of conception do not pass.

Medical abortion at 10 to 13 weeks gestation

Where medical abortion can be offered, those women with pregnancies of 10 to 13 weeks completed gestation would have 200 mg mifepristone administered in the clinic and arrangements made for admission 1-3 days later to a clinical area where anti emetics and analgesics may be administered according to a nurse initiated protocol as required during the abortion. Blood will be taken for group and hold and misoprostol micrograms per vagina or sublingually administered followed by up to 2 further doses of misoprostol 400 micrograms at three hour intervals (as required) until bleeding and contractions are initiated. Women will remain fasting in the clinical area until products of conception have passed and ultrasound has demonstrated that there is no significant amount of tissue remaining in the uterus. Those who have not passed the pregnancy sac within 6 -8 hours (expected rate 1: 20 as observed amongst 4036 women given this drug combination Ashok, Kidd et al 2002:10) will be managed according to their clinical situation and personal preferences. Those with heavy bleeding or significant pain will be offered immediate surgical evacuation. Those with lesser degrees of bleeding or pain may be offered overnight admission followed by a second attempt at medical abortion next day. Those with no bleeding may be discharged to home with arrangements for readmission for medical or surgical abortion at a later date. Where the sac has passed but ultrasound demonstrates retained products of conception in the uterine cavity, women who are not bleeding heavily may be discharged to home with 6 x 200 microgram misoprostol tablets to be taken with meals tds and instructed to return to a follow up clinic for ultrasound confirmation of completed abortion in 7 days time.

Monitoring

Every woman choosing medical abortion with mifepristone will be invited to consent to a review of her medical records within 12 months following treatment. Where any encounter diagnosis suggests a post treatment complication, a review of the paper medical record will be undertaken to allow an audit of any adverse outcomes treated in public hospitals.

Attachment 2:

PROTOCOL FOR EARLY MEDICAL ABORTION USING MIFEPRISTONE

- All patients must be referred with a letter from the referring doctor including name, address and provider number and a statement of why the woman is being referred for abortion.

- An initial consultation will establish why the woman is requesting abortion and that the grounds for abortion fall within those defined for legal abortion in [redacted]. If further counselling about abortion or alternatives seems appropriate this will be provided or arranged.

- An appropriate medical history will be taken; discussion of future contraception and of Pap smear screening will be offered. Gestation of the pregnancy and the fact that the pregnancy is intra-uterine will be confirmed by ultrasound. Haemoglobin level, FBC and blood group will be determined.

- The options of medical and surgical abortion will be discussed with the woman. Medical abortion is only possible if the pregnancy is of nine weeks' duration or less i.e. 63days from the date of the last menstrual period. **Medical abortion with mifepristone/misoprostol will only be offered to women suffering from life-threatening or otherwise serious illnesses or conditions, where continuing the pregnancy poses greater risks to the women's life or health than does induced abortion. The intended population in terms of medical conditions is as follows:**

- **Hypertensive disorders including essential and secondary hypertension, history of severe pre-eclampsia or eclampsia in previous pregnancy/pregnancies**
- **Chronic renal disease**
- **Diabetes both Type 1 and Type 2 requiring medication**
- **Cardiac disease including congenital, rheumatic and coronary artery disease**

- **Auto-immune disorders including but not limited to systemic lupus, anti-cardiolipin antibodies, thyroiditis, ITP etc**
- **Breast cancer; other cancers where major surgery and/or chemotherapy or radiotherapy is indicated**
- **Previous history of thrombo-embolism**
- **Epilepsy especially where multiple anti-convulsant therapy is required**
- **Severe neurological disorders**
- **Severe psychiatric disorders including but not limited to previous puerperal psychosis, depression or history of depression, suicidal tendency**
- **Severe liver disease**
- **Other serious medical conditions not included within this list which in the opinion of the practitioners constitute a threat to the life or a serious threat to the health of the woman**

This restriction is consistent with subregulation 12B (2) of the Therapeutic Goods Regulations 1990.

- In some cases it will be appropriate for the woman to have both mifepristone and misoprostol administered in the hospital and for the woman to remain in the hospital until the abortion process is complete. In others it may be both possible and appropriate for the medical abortion process to occur at home. In the latter situation it is essential that a designated support person stays with the woman until the abortion process is complete and that the support person is able to bring the woman back to the hospital if emergency care is required.

- If a woman expresses interest in medical abortion the procedure will be fully explained to her including the risks. Where a woman is planning to undergo the abortion process at home the need to stay in [redacted] until the abortion process is complete and the fact that she will require an adult support person to be with her during the process will be explained. Every woman will be given a patient information leaflet. Discussion with the doctor will then determine

whether medical abortion is the most appropriate option for the particular woman.

- The woman must read and sign a consent form for medical abortion.

- Subsequently the woman will be supplied with 200 mg mifepristone and will take the medication in direct view of [redacted]. She will also be prescribed 1 gram metronidazole and one gram azithromycin or other antibiotic if vaginal swab results indicate this to be appropriate.

- 48 hours later she will again attend at [redacted] and will have 800 µg misoprostol inserted vaginally. If it is intended that the abortion process take place in hospital she will remain in the hospital until that is complete. If it has been decided that the abortion process will take place at home she will be free to leave after misoprostol insertion but must undertake to stay in [redacted] with her support person until the process is complete. For most women the process will occur within 4-6 hours. Where this is not the case further vaginal insertion of 400 µg misoprostol will be performed.

- Women will be supplied with a prescription for suitable analgesia. Rhesus negative women will be given anti-D.

- Women undergoing the abortion process at home will be informed that they can contact or return to the hospital at any time should heavy bleeding, fever or any other problem or concern arise.

- A follow-up appointment will be arranged within two weeks post-abortion at which ultrasound will be used to confirm that the abortion is complete and future contraception will be discussed.

- Appropriate medical records will be maintained at all times. Outcomes, side effects and any adverse events will be noted and results audited at intervals of six months.

PROTOCOL FOR MEDICAL ABORTION USING MIFEPRISTONE IN 2ND AND 3RD TRIMESTERS

- An initial consultation with [redacted] will establish why the woman is requesting abortion and that the grounds for abortion fall within those defined for legal abortion in [redacted]. If further counselling about abortion or alternatives seems appropriate this will be provided or arranged.

- An appropriate medical history will be taken. Haemoglobin level, FBC and blood group will be determined if this has not already been done .

- The abortion process will be discussed in detail with the woman and written information provided. The woman will be informed that retained placenta sometimes occurs following medical abortion in the 2nd and 3rd trimesters and that if this happens then removal under general anaesthesia may be required. **Medical abortion with mifepristone/misoprostol will only be offered to women suffering from life-threatening or otherwise serious illnesses or conditions, where continuing the pregnancy poses greater risks to the women's life or health than does induced abortion. The intended population in terms of medical conditions is as follows:**

- **Hypertensive disorders including essential and secondary hypertension, history of severe pre-eclampsia or eclampsia in previous pregnancy/pregnancies**
- **Chronic renal disease**
- **Diabetes both Type 1 and Type 2 requiring medication**
- **Cardiac disease including congenital, rheumatic and coronary artery disease**
- **Auto-immune disorders including but not limited to systemic lupus, anti-cardiolipin antibodies, thyroiditis, ITP etc**
- **Breast cancer; other cancers where major surgery and/or chemotherapy or radiotherapy is indicated**

- **Previous history of thrombo-embolism**
- **Epilepsy especially where multiple anti-convulsant therapy is required**
- **Severe neurological disorders**
- **Severe psychiatric disorders including but not limited to previous puerperal psychosis, depression or history of depression, suicidal tendency**
- **Severe liver disease**
- **Other serious medical conditions not included within this list which in the opinion of the practitioners constitute a threat to the life or a serious threat to the health of the woman**

This restriction is consistent with subregulation 12B (2) of the Therapeutic Goods Regulations 1990.

- The woman must read and sign a consent form for medical abortion.

- The woman will have mifepristone 200mg administered orally under the direct vision of [redacted] Following this, unless there are medical contra-indications requiring that the woman remain as an in-patient in hospital, she may go home or to stay elsewhere in [redacted] provided she has the means to return immediately to the hospital if concerns arise. At a mutually arranged time 24-48 hours following ingestion of the mifepristone dose the woman will return to [redacted] for admission as an in-patient in the gynaecology ward. She will then have 800μgm misoprostol administered vaginally, either by [redacted] or by another suitable accredited member of the staff of the [redacted]. She will be closely monitored and supported by nursing staff. She will be reviewed by a member of the medical staff 4-6 hours following administration of misoprostol. If uterine contractions are not well established then a further 400μgm misoprostol may be administered vaginally. This may be repeated up to a total of five doses of 400μgm misoprostol if needed. In general it is expected that the abortion process will occur within 8 hours of the first dose of misoprostol.

- The woman will be prescribed 1 gram metronidazole and one gram azithromycin or other antibiotic if vaginal swab results indicate this to be appropriate.

- Women will be offered suitable analgesia including narcotics during the abortion process. Rhesus negative women will be given anti-D.

- A follow-up appointment should be arranged two to six weeks post-abortion at which the woman's experience will be reviewed and any information e.g. findings of autopsy results for the fetus discussed with herself and her partner.

- Appropriate medical records will be maintained at all times. Outcomes, side effects and any adverse events will be noted and results audited at intervals of six months.

Attachment 2:

[redacted] have been authorised to prescribe mifeprsitone for the following indications;

- Medical abortion in the first trimester
- Medical abortion in the second trimester
- Cervical priming prior to surgical abortion in the first and second trimesters

We each seek to renew authorisation to prescribe and to vary the protocols for administration of misoprostol, allowing greater flexibility in the interval between mifepristone and misoprostol administration in the three non surgical protocols.

Our arrangements for pre abortion counselling, contraceptive education, after hours support and follow up remain unchanged. We have removed reference to these from the following protocols for administration of medicines.

Medical abortion up to 63 days from last menstruation

Mifepristone 200mg oral stat and misoprostol 800 micrograms per vagina, sublingual or buccal administered in the clinic between 0 and 72 hours after mifepristone. Discharge to home with a further 6 x 200micrograms misoprostol tablets. These are to be taken orally 200 micrograms three times per day on the subsequent 2 days if there are symptoms of incomplete abortion (heavy bleeding per vagina and/or cramping pelvic pain).

Misoprostol may be administered at a range of times following mifepristone administration. The protocol which we initially submitted and which was approved for our use required 200 mg mifeprsitone to be administered at the same time as 800 micrograms of misoprostol (0 hours delay). This method has been demonstrated to produce complete abortion in 95% of cases (Creinin et al 2007). In [redacted] there was 1 treatment failure following 176 early medical abortions conducted using this regimen.

The more recent protocol for administration which was approved for our use is the one endorsed by the RCOG (2004). This protocol includes administration of misoprostol 24 to 48 hours after mifepristone administration. There were no treatment failures amongst 323 early medical abortions conducted in [redacted] using this regimen.

Misoprostol administration may also be delayed up to 72 hours after mifepristone administration. Schaff et al (2000) reported a 96% completed abortion rate amongst 772 women who had mifepristone followed by 400 micrograms of vaginal misoprostol at 72 hours, this did not differ from the completed abortion rate in two comparison groups where misoprostol was administered at 24 or 48 hours. More recently Heikinheimo, Leminen & Suhonen (2007) have presented a series generated when a Swedish clinic offered a choice of regimens with misoprostol given at 24, 48 or 72 hours. Amongst the 260 women who selected the 72 hour delay from mifepristone to misoprostol treatment, the completed abortion rate was 93.1% and this did not differ significantly from the completed abortion rate following mifepristone to misoprostol delays of 24 or 48 hours.

Because mefipristone 200 mg may be followed by misoprostol 800 micrograms at 0 to 72 hours and still be highly effective in interrupting pregnancy, we believe that it is appropriate to allow this flexibility when planning care. Women need to plan to set aside a day to stay at home following misoprostol administration and they appreciate the opportunity to select which day this will be.

We also seek to vary the regimen for early treatment of retained products of conception with additional doses of misoprostol on days subsequent to the initial dose of 400 micrograms. Our currently approved protocol includes further doses of 400 micrograms of misoprostol daily on the 3 days after the initial dose of misoprostol. We prefer to administer the same total dose of misoprostol (6 x 200 microgram tablets oral) as one tablet three times per day for two days. This is the treatment for retained products of conception following surgical abortion which is widely used in [redacted] and it is familiar to the wide range of clinicians who may be consulted by a woman during the days after her medical abortion (Chambers & Mulligan 2008).

Medical abortion up 13 weeks gestation

Mifepristone 200mg administered in the clinic and arrangements made for admission within the following 72 hours to a clinical area where misoprostol 400 micrograms per vagina or sublingually will be administered, followed by misoprostol 400 micrograms at three hour intervals (up to 2 further doses as required) until bleeding and contractions are initiated.

Medical abortion over 13 weeks gestation

Mifepristone 200mg oral administered followed by admission within the next 72 hours for induction of labour using 800 micrograms of misoprostol per vagina and further doses of 400 micrograms every 3 hours to a maximum of four doses.

This protocol has been varied to allow induction of labour with misoprostol to begin at any time within 72 hours of mifepristone administration (rather than at 6 - 72 hours). This misoprostol regimen is standard for misoprostol only induction of labour abortion in [redacted] teaching hospitals.

Cervical ripening prior to surgical abortion

Mifepristone 200mg oral administered hours or days prior to admission for surgical dilation and curettage (first trimester abortion) or dilation and evacuation of the uterus (second trimester abortion). Pre operative cervical ripening will also be undertaken using misoprostol according to established protocols.

This protocol remains unchanged since we were first approved to use it in October 2008.

Please find attached;

- HREC support letters for each medical practitioner
- Agreement to treatment directions signed by each medical practitioner
- Research evidence supporting changes to the protocols for timing of misoprostol administration

Thank you for attending to our applications.

[redacted]

[redacted]

abortion: medical

1. Purpose

When termination of pregnancy is the agreed course of action beyond 18 weeks gestation, [redacted] offers only medical termination of pregnancy.

The following guidelines apply to all patients admitted for termination of pregnancy after 18 weeks gestation, including induction of labour for fetal death in utero (FDIU) and some cases from 14-18 weeks gestation.

2. Definitions

FDIU: Fetal death in utero

[redacted]

Medical abortion: Procedure using a combination of the drugs mifepristone and misoprostol to induce expulsion of a pregnancy

3. Responsibilities

Birth Suites midwifery/medical team: management of the procedure on the day(s) of induction including administration of misoprostol

[redacted] **clinicians**: documentation including obtaining consent before carrying out clinical procedures

[redacted] **Head of Unit**: primary responsibility for use of mifepristone within [redacted] contact for problems related to use of mifepristone, oversee data collection

[redacted] **Coordinator**: follow procedure for administration of mifepristone and coordinates booking and follow-up of woman

Midwifery Team Leader: liaison with multidisciplinary team

4. Procedure

Assessment of need

In the event of medical termination of pregnancy for fetal anomaly, women will be seen and referred by the [redacted] team following appropriate assessment within current [redacted] guidelines.

The assessment of need is to be undertaken by the treating medical practitioner in consultation with the woman after appropriate testing and counseling has occurred and results/reports provided to the attending practitioner. The attending practitioner may need to consult further with other relevant specialists as part of the assessment.

Indications for use of mifepristone

- Women having termination of pregnancy at an advanced gestation (between 18 and 28 weeks and some cases from 14-18 weeks gestation), when [redacted] does not offer surgical abortion and the current alternative is medical management with misoprostol alone.

- Fetal death in utero at any gestation

In addition women need to:

- currently reside within 1 hour traveling time of the [redacted]
- have access to transport (car)
- have access to a telephone
- mifepristone and misoprostol will be administered under direct supervision on site at [redacted]

Contra-indications

Absolute contra-indications to medical abortion

- suspected ectopic pregnancy
- haemorrhagic disorder or current anticoagulant therapy
- known sensitivity to prostaglandins, mifepristone or any component of the products
- porphyria

- chronic adrenal failure
- severe asthma not controlled by therapy
- epilepsy
- any woman who does not want a termination
- no valid consent

Relative contra-indications to medical abortion: requires consultation

- use of oral corticosteroids - long term or current treatment
  - For women with asthma using inhaled corticosteroid therapy, it is recommended that the steroid dose be doubled during the 48 hours preceding the administration of mifepristone and continued for one week post TOP.
- Hb < 100 grams per decilitre
- IUCD in situ
- history of cardiac disease
- women over 35 years of age who also smoke >10 cigarettes per day
- multiple uterine scars (>2 caesarean sections or myomectomy)
- In the absence of specific studies:
  - Breastfeeding: Although it is not known whether misoprostol is excreted in human milk, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause diarrhoea in nursing infants. As a precaution, breastfeeding women should avoid treatment or discharge the breast milk for 2-3 days.
  - renal failure, liver failure or malnutrition

Absolute social contra-indications

- unable to give informed consent due to persistent indecision about having an abortion
- unwillingness to proceed to appropriate alternative forms of medical TOP if necessary
- persistent and significant psycho– social issues
- credible evidence of threats or coercion in making her decision

Risks and precautions

Medical risks

- retained placenta
- haemorrhage
- uterine rupture
- disseminated intravascular coagulation (DIC)
- infection
- drug reaction
- fetal abnormality may occur after misoprostol has been administered if pregnancy not aborted
- hysterectomy

Social/emotional and cultural risks

- social as well as cultural risks to the woman may exist whether she elects to terminate her pregnancy or to continue
- possible disapproval for her decision within her immediate support systems, physical and cultural communities
- fear of disapproval resulting in isolation from friends and family
- lack of direct telephone access
- transportation problems

PRE PROCEDURE: PRIOR TO DAY ONE

Patient Information/Consent

Written consent is to be obtained by the treating medical practitioner before a pregnancy termination is performed. The clinician will ensure that the woman is fully informed about the procedure; including who will perform it and possible adverse effects.

Note: Current procedures apply with the addition of **consent for medical abortion.**

Documentation

- [redacted] fetal abnormality proforma
- TOP proforma

- consent form
- prescription for mifepristone
- patient Information "Mifepristone and Misoprostol for Medical Termination of Pregnancy explained and given

DOSAGE(medications are prescribed fully)
Establish the woman's allergy status, blood group and rhesus status.

Gestation	Medication
13-24 weeks gestation:	• 200mg ***mifepristone*** orally, swallowed under supervision • 36-48 hours later 800 micrograms **misoprostol** administered vaginally • Further doses of 400 micrograms **misoprostol** administered orally at 3 hourly intervals up to a maximum of four doses if products of conception not passed. • Consideration of a repeat course of treatment if unsuccessful.
After 24 weeks gestation:	• As for 13-24 weeks gestation, but dosage of misoprostol may be reduced and intervals increased as judged appropriate by the clinician.

Bookings (two appointments)
Ensure that the woman receives appointment times that are scheduled according to her needs which will be accommodated as much as practically possible.

1. Appointment with FMU Coordinator for mifepristone administration
- This appointment will be made by the consultant in direct consultation with [redacted]. The Bereavement Care worker (contact Pastoral Care & Spirituality Services: page or phone [redacted]) to be informed of date and time of appointment for administration of mifepristone.

2. Appointment for admission to birth suite for administration of misoprostol
All terminations are to be booked by the [redacted] in consultation with the [redacted] who will ensure the relevant pre-admission procedures have been completed and will arrange bed allocation.

Documentation
- Woman is given contact details for [redacted] and instructed to report to the reception desk in [redacted] when presenting for mifepristone (and ask the clerk to page [redacted]).
- Woman is given documentation (step by step guide) with the details of all appointments.

Mifepristone administered	Admission to birth suite for misoprostol at 07.00 hours
Monday	Wednesday
Tuesday	Thursday
Wednesday	Friday

DAY ONE
[redacted] to collect mifepristone from pharmacy on the day ([redacted] is booked for administration of mifepristone).

Administration of mifepristone
Woman presents to [redacted] who will explain the procedure and check that:
- the woman is prepared to go ahead with the termination
- the consent form has been signed
- all medications have been prescribed in full
- the woman's admission date is arranged
- the bereavement care worker is available and informed
- baseline observations: pulse, temperature, blood pressure taken

Medication administration: mifepristone 200mg orally is administered by the FMU Coordinator [redacted] to ensure that:
- documentation is complete and located in the woman's medical record

- the written instruction sheet has been provided and discussed with the woman
- the woman is discharged home after receiving her mifipristone and is aware that she must return in 36-48 hours for Day 3 administration of misoprostol
- following administration of mifepristone the woman may leave the hospital
- during this time she may wish to speak to the bereavement care worker
- if remaining in the area a suitable quiet space should be allocated for her to wait

DAY TWO

Woman remains at home with clear instructions when to contact the hospital.

DAY THREE

Birth suite medical staff informed woman is booked for medical abortion by [redacted]

Admission
The woman attends the hospital Admissions desk at 07.00, is admitted to birth suite (this equates with 48hours post administration of mifepristone).

If the woman has any symptoms (prior to the arranged re-admission date and time) (as per consumer information) she attends the hospital Emergency Department triage desk and will then be admitted to birth suite.

Care of the Woman
As per management plan.
Note: 90% of women are expected to abort within 15 hours of commencement of prostaglandin.

Medication administration
Analgesia may be administered as prescribed by the medical practitioner, 15 minutes prior to the administration of the first dose of misoprostol.

A vaginal exam is performed and the following prescribed medication administered:

- misoprostol 800 micrograms administered vaginally (PV)
- further doses of 400 micrograms misoprostol are administered orally at 3 hourly intervals up to a maximum of four doses if products of conception are not passed.

Note: Concurrent use of antiemetics may reduce gastrointestinal side effects. Alternatively the woman may elect to receive the treatment (misoprostol) vaginally if preferred, to reduce side effects.

If the treatment regime is unsuccessful, consideration should be given to a repeat course of treatment (discuss with medical practitioner and woman). Refer to section: Day Four.

Analgesia
Apart from the initial dose of analgesia given prior to the first dose of misoprostol, the regime will vary according to the individual needs of the woman.

Antiemetics
Antiemetics should be prescribed by the medical practitioner to include for example: *metoclopramide 10 milligrams IV, IM or PO, 6 hourly PRN* and other antiemetics as appropriate.

Documentation
Complete all necessary documentation including the ***Mifepristone data form***

Post delivery / birth

If there is complete delivery of fetus and placenta **3rd stage management will be the same as for a normal vaginal birth.**

- vital signs, fundal level and PV bleeding are checked after the delivery of the placenta and
- the woman is given an opportunity to shower and offered something to eat and drink

- if required: collect maternal blood for maternal fetal haemorrhage test (FMH) and administer anti-D according to [redacted] CPG: Rh D Immunoglobulin in Obstetrics
- The woman may or may not wish to see her fetus / baby (her terminology is used) at or after delivery / birth.
- If the fetus weighs > 400gm or post 20 weeks gestation, as determined by the first certifier, the Birth / Death Registration forms must to be completed by a medical practitioner.
- Midwife caring for the woman discusses disposal of fetus and ensures this happens with the woman's wishes and in accordance with [redacted] procedure: Tissue: Disposal of human tissue not for pathological examination.

- Contraception is recommended during the next menstrual cycle following fetal expulsion to decrease potential exposure of a subsequent pregnancy to mifepristone.
  - Midwife ensures the woman is prescribed her chosen contraception method and understands the method

of use.

- Midwife ensures all documentation has been completed including: Bereavement Care Plan, observation chart and required data form.

The midwife / medical practitioner caring for the woman has access to debrief/supervision session within 24 hours of delivery as requested.

Follow-up Appointments

- Follow-up appointments will be arranged as required in consultation with the [redacted].
- Ensure the woman is given the name and contact details of a hospital support person (midwife, social worker, Pastoral Care and Spirituality Services worker, genetic counsellor, medical practitioner) to contact if required prior to the next appointment.

Exceptions to the above procedures

Women with >2 lower uterine segment caesarean section (LUSCS) or myomectomy scars need to be individually discussed with the consultant prior to administration of mifepristone / misoprostol.

Failure to deliver on day 3

The nurse/midwife will contact the registrar if the fetus and/or placenta have not been delivered within 15 hours. A medical review is required.

If the fetus has not delivered within 15 hours, the following procedure should be followed:

- A vaginal examination will be performed by the attending midwife to determine cervical dilatation and the Registrar will be alerted as to the status of the woman.
- An additional dose of 200mg mifepristone orally is administered 15 hours after the first dose of misoprostol.

DAY FOUR

- Following medical review, the woman will be administered misoprostol 800 micrograms vaginally followed by 400 micrograms every three hours for a maximum of **three** doses (total).
- If the fetus is undelivered by the 3rd dose, a vaginal examination will be performed by the attending midwife, followed by medical review.
- The recommendation may be to continue according to the regime in Appendix 1: Day 4, OR to progress to extra-amniotic infusion. Each case / woman will be managed by medical staff following individual assessment.

Retained placenta: The Registrar must be notified within 30 minutes post delivery of the fetus if the placenta has not delivered (AND the woman is haemodynamically stable AND not actively bleeding).

The management for retained placenta with regard to mid trimester abortion is as follows:

- One dose misoprostol 400 micrograms orally
- Syntocinon 40units in 1 litre normal saline administered intravenously at a rate of 25millilitres/hour via pump is commenced if there is excessive bleeding.
- Woman is nil orally, commenced at the delivery/birth of the fetus and continues until the placenta has been delivered and blood loss is within normal limits.
- If the placenta is retained, the woman will require a manual removal of placenta, either under general anaesthetic in theatre or under regional anaesthetic.
- Record fluid balance including vaginal loss.

5. Appendices

Appendix 1: Summary of mifepristone / misoprostol administration

DAY 1

Drug	Dose	Route	Timing
mifepristone	200 milligrams	Orally (PO)	once only

DAY 2 (woman remains at home)

DAY 3 (36-48 hours after Day 1)

Drug	Dose	Route	Timing
misoprostol (1st dose)	800 micrograms	PV	Initial dose

misoprostol (2nd dose)	400 micrograms	PO	3 hours after initial dose
misoprostol (3rd dose)	400 micrograms	PO	6 hours after initial dose
misoprostol (4th dose)	400 micrograms	PO	9 hours after initial dose
misoprostol (5th dose)	400 micrograms	PO	12 hours after initial dose

- Following medical review the following medication is to be administered :

Drug	Dose	Route	Timing
mifepristone	200 milligrams	Orally (PO)	15 hours post initial misoprostol dose

DAY 4 (if delivery / birth has not occurred)

Drug	Dose	Route	Timing
misoprostol (1st dose)	800 micrograms	PV	Initial dose
misoprostol (2nd dose)	400 micrograms	PO	3 hours after initial dose
misoprostol (3rd dose)	400 micrograms	PO	6 hours after initial dose
Hold remaining doses and contact Registrar for further instruction			
misoprostol (4th dose)	400 micrograms	PO	9 hours after initial dose
misoprostol (5th dose)	400 micrograms	PO	12 hours after initial dose

If the fetus is not delivered after 15 hours:

- The Registrar is contacted
- A medical review is required

Appendix 2: Quick Guide for Mifepristone/ Misoprostol Regimens at [redacted]

Gestation / Protocol	Up to 63 days (<9 weeks)	63- 91 days (9-13 weeks)	13- 24 weeks	> 24 weeks
Mifepristone (taken under supervision)	**200mg orally**	**200mg orally**	**200mg orally**	**200mg orally**
Interval	36-48 hours (1-3 days acceptable)	36-48 hours (1-3 days acceptable)	36-48 hours (1-3 days acceptable)	36-48 hours (1-3 days acceptable)
1st Dose of misoprostol	**800 micrograms** orally or vaginally	**800 micrograms** orally or vaginally	**800 micrograms** orally or vaginally	**800 micrograms** orally or vaginally
Interval	4-6 hours	3 hourly	3 hourly	3-6 hourly at discretion of clinician
Repeat doses of misoprostol	**One dose only** - 400 micrograms misoprostol vaginally if products not passed	**Up to 5 doses** of 400 microgram misoprostol vaginally if products not passed	**Up to 4 doses** of misoprostol 400 microgram vaginally if products not passed	Dose may be reduced at clinician's discretion
Further treatment			Consider repeat course of treatment	Consult with senior medical practitioner

Appendix 3: Absolute and relative contraindications

Contraindications	Relative Contraindications

• chronic adrenal insufficiency, • severe uncontrolled asthma, • porphyria, • suspected ectopic pregnancy • hemorrhagic disorder or current anticoagulant therapy • known sensitivity to prostaglandins, mifepristone or any component of the products, • epilepsy	• use of oral corticosteroids • Hb < 100 grams per decilitre • IUCD in situ • history of cardiac disease • > 35 years of age & >10 cigarettes per day. • multiple uterine scars (>2 caesarean sections or myomectomy) • renal failure, liver failure or malnutrition

Appendix 4: Procedure summary

Use of mifepristone for termination of pregnancy: procedure summary (30kb pdf)

6. Performance Indicators

7. [redacted] Related polices, procedures and documentation

Policies and Procedures
Reproductive Loss: Stillbirth 20 weeks and over
Reproductive Loss Pre 15 weeks and 15-20 weeks
Reproductive Loss: Pre 20 week/stillbirth/neonatal death/infant death
Tissue: Disposal of human tissue not for pathological examination

Clinical Practice Guidelines (CPG)
Termination Review Process (Intranet only)

Documents and forms
- Fetal Abnormality Proforma
- Termination of Pregnancy Proforma
- Consent form – Medical Termination with Mifepristone
- TGA authorization for use of Mifepristone
- Labour and Delivery Plan (Fetal Abnormality)
- Mifepristone data form
- Bereavement Care Plan (MR/90400)
- Frequent Observation and Fluid Balance Chart (MR/43066)
- refer to: Reproductive Loss Resources - contains link to revised Bereavement Response Manual.

8. Reference Documents

- Lund K, Shand C. Second trimester medical abortion: Level J Procedure, Capital & Coast District Health Board New Zealand Guideline Manual 2007

- Royal College of Obstetricians and Gynaecologists. The Care of Women Requesting Induced Abortion, Evidence-based Clinical Guideline Number 7 September 2004

[redacted]

Policy and Procedure Manual

Use of Mifepristone for Termination of Pregnancy – [redacted] Pathway

Procedure Summary

Day 0	Day 1	Day 3	Discharge
Woman requests and agrees to TOP ***Clinician*** **DOCUMENTATION** ▪ fetal abnormality proforma ▪ TOP proforma ▪ consent for: • mifepristone and misoprostol ▪ labour and delivery/birth plan ▪ Mifepristone Database Worksheet **BOOKING** ▪ liaise with [redacted] re: bookings for: 1. mifepristone administration 2. admission to birth suite for misoprostol **CHART MEDICATIONS** ▪ mifepristone, misoprostol ▪ analgesia ▪ antiemetic **PATIENT INFORMATION** ▪ Give and discuss information –Medical termination of pregnancy ***FMU Coordinator*** ▪ book appointments ▪ complete appointment information in the patient information and give to patient ▪ notify bereavement worker of appointment times	Woman presents to [redacted] and asks for [redacted] [redacted] paged [redacted] ▪ arrange collection of mifepristone from pharmacy ▪ administer mifepristone 200mg orally ▪ complete mifepristone database worksheet ▪ reinforce consumer instructions / appointment information including: • oral analgesia • when to contact the hospital ▪ contact Bereavement worker ▪ discharge woman	Patient admitted to birth suite at 7.00 am ***Midwife and Doctor*** ▪ misoprostol 800ug PV stat ▪ 3/24 400micrograms orally or PV x4 doses ▪ usual care ***If not delivered after 4 doses*** repeat above protocol once ***If not delivered after 2nd course*** Review by Registrar Consider: ▪ further misoprostol ▪ intra-amniotic PG ▪ a catheter	▪ Death +/- Birth Certificate to be completed by staff on shift of patient delivery ▪ complete mifepristone database worksheet ▪ woman to be seen by • Bereavement worker • Medical ▪ autopsy consent ▪ analgesia ▪ contraception ▪ anti D ▪ follow-up appointment

Attachment 2:

Medical Abortion Workplace Instruction

Description: Medical Abortion using Mifepristone and Misoprostol

Target Audience: Sexual Health Nursing and Medical Staff

Related Policy/Procedure:

1. Patients can be referred with a letter from the referring clinician, or can self-refer.
2. An initial consultation will establish why the woman is requesting abortion and that the grounds for abortion fall within those defined for legal abortion in the [redacted] If further counselling about abortion or alternatives seems appropriate this will be provided or arranged.
3. An appropriate medical history will be taken, and discussion of future contraception and of Pap smear screening will be offered. Sexually transmitted infection testing will also be offered and should be encouraged. Gestation of the pregnancy and the fact that the pregnancy is intra-uterine will be confirmed by ultrasound. Haemoglobin level and blood group will be determined.
4. The options of medical and surgical abortion will be discussed with the woman. Medical abortion is only possible if the pregnancy is of 9 weeks' duration or less, i.e. 63 days from the first day of the last menstrual period.
5. If a woman expresses interest in medical abortion the procedure will be fully explained to her including the risks, the need to be able to access medical care until the abortion process is complete, and the fact that she will require an adult support person. She will be given a patient information leaflet. Discussion with the doctor will then determine whether medical abortion is the most appropriate option for the particular woman. Only women 16 years of age and over will be considered for medical abortion.
6. Two doctors must agree that medical abortion is indicated for the woman.
7. The woman must read and sign a consent form for medical abortion.
8. The woman should be offered further clinical support from a member of the nursing staff.
9. Day 1: At a mutually convenient time the woman will be supplied with 200mg mifepristone and will take the medication in direct view of the doctor. In rare situations it may be appropriate for the women to self-administer this oral dose of mifepristone at her home.

[redacted]

[redacted]

10. Day 2-3: The woman will have 800µg misoprostol inserted vaginally, either by the doctor or by herself. She must undertake to remain within easy access of medical care until the abortion process is complete. For most women the abortion will occur within four hours. Where this is not the case the woman will contact the service for advice regarding possible vaginal insertion of a further 400 µg misoprostol.
11. Day 2-5: Anti D immunoglobulin (250IU) will be given to Rhesus negative women via intramuscular injection.
12. Women will be supplied with a prescription for suitable analgesia.
13. Women will be supplied with a telephone number for 24 hour emergency contact, to be used should heavy bleeding, fever, or any other problem or concern arise at any time.
14. Approximately four weeks post vaginal bleeding, assess for completion of abortion using urine B-HCG. If this is negative the abortion is taken to be complete. If positive, a quantitative serum B-HCG measurement should be performed, and if high or increasing from baseline an ultrasound examination should be arranged.
15. If the ultrasound reveals an incomplete abortion, surgical abortion should be offered.
16. Appropriate medical records will be maintained at all times. Outcomes, side effects, and any adverse events will be noted and results audited at intervals of 12 months.
17. Members of the [redacted] staff who have ethical, moral, or religious objections to abortion should not be compelled to take part in performing the medical abortion, but are expected to treat the woman in a professional and non-judgemental manner.

Evaluation Method:

Activity(ies) that will be used to assess for effectiveness/efficiency

Evaluation will be done as per next review date or when changes occur

Developed By: [redacted]	**Last Review Date:** 29/09/2010
Authorised By: [redacted]	**Next Review Date:** 01//07/2011
.....	**Effective Date:**

Attachment 2:

5/11/10

Re: Five medical practitioners practicing at the [redacted] covered by the [redacted] seek to renew authorisation to prescribe mifeprsitone for a further 24 months.

[redacted] have been authorised to prescribe mifeprsitone for the following indications;

- Medical abortion in the first trimester
- Medical abortion in the second trimester
- Cervical priming prior to surgical abortion in the first and second trimesters

We each seek to renew authorisation to prescribe and to vary the protocols for administration of misoprostol, allowing greater flexibility in the interval between mifepristone and misoprostol administration in the three non surgical protocols.

Our arrangements for pre abortion counselling, contraceptive education, after hours support and follow up remain unchanged. We have removed reference to these from the following protocols for administration of medicines.

Medical abortion up to 63 days from last menstruation

Mifepristone 200mg oral stat and misoprostol 800 micrograms per vagina, sublingual or buccal administered in the clinic between 0 and 72 hours after mifepristone. Discharge to home with a further 6 x 400micrograms misoprostol tablets. These are to be taken orally 200 micrograms three times per day on the subsequent 2 days if there are symptoms of incomplete abortion (heavy bleeding per vagina and/or cramping pelvic pain).

Medical abortion up 13 weeks gestation

Mifepristone 200mg administered in the clinic and arrangements made for admission within the following 72 hours to a clinical area where misoprostol 400 micrograms per vagina or sublingually will be administered, followed by misoprostol 400 micrograms at three hour intervals (up to 2 further doses as required) until bleeding and contractions are initiated.

Medical abortion over 13 weeks gestation

Mifepristone 200mg oral administered followed by admission within the next 72 hours for induction of labour using 800 micrograms of misoprostol per vagina and further doses of 400 micrograms every 3 hours to a maximum of four doses.

Cervical ripening prior to surgical abortion

Mifepristone 200mg oral administered hours or days prior to admission for surgical dilation and curettage (first trimester abortion) or dilation and evacuation of the uterus (second trimester abortion). Pre operative cervical ripening will also be undertaken using misoprostol according to established protocols.

These protocols have been reviewed and their use is now supported by the [redacted] and the [redacted].

Please find enclosed:

1) [redacted] support letters for each of 5 medical practitioners
2) Agreement to Treatment Directions forms signed by 4 medical practitioners. [redacted] is currently on leave. Her form will be forwarded separately as soon as practicable.

Thank you for considering our applications

[redacted]

Attachment 2:

Mifepristone and misoprostol for medical termination of pregnancy in the first and mid trimesters of pregnancy

Indications and regimens for prescription and use of the unapproved product mifepristone, 200mg tablets at the ([redacted])

2/05/11

Indications for use of mifepristone

Termination of pregnancy where medical abortion is assessed clinically as the most appropriate method for the woman, including when surgical abortion is not advisable. These medications will be used when continuation of the pregnancy constitutes a risk to the mother's life – as per [redacted] law and will include first and mid trimester termination pregnancies afflicted by severe congenital fetal abnormalities incompatible with long term fetal survival. Terminations will be carried out according to the [redacted]:

Site of prescription and use

Care will be provided at [redacted] Specifically the mifepristone and misoprostol will be administered under direct supervision at [redacted]. It is anticipated that the vast majority of women treated will proceed to complete the abortion on the premises. In exceptional cases, if abortion does not occur or is not complete within a few hours of misoprostol, outpatient follow up will be arranged, or transfer to another institution, staffed and equipped to conduct pregnancy termination.

Regimens to be used

The following regimens will be used, as recommended by the Royal College of Obstetricians and Gynaecologists (RCOG), as also reported in several large case series.

Up to 63 days gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- A further dose of 400 µg misoprostol administered orally or vaginally if products of conception not passed within 4-6 hours.

63-91 days gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- Further doses of 400 µg misoprostol administered orally or vaginally at 3 hourly intervals up to a maximum of five doses if products of conception not passed.

13-24 weeks gestation:

- 200mg mifepristone orally, swallowed under supervision

- 36-48 hours later 800µg misoprostol administered vaginally
- Further doses of 400 µg misoprostol administered orally at 3 hourly intervals up to a maximum of four doses if products of conception not passed.
- Consideration of a repeat course of treatment if unsuccessful.

After 24 weeks gestation:

- As for 13-24 weeks gestation, but dosage of misoprostol may be reduced and intervals increased as judged appropriate by the clinician.

Since this protocol was published there has been a growing body of evidence supporting the efficacy of sublingual administration of misoprostol as an alternative route to oral or vaginal administration.

Potential variations may be made according to clinical judgment in individual cases, or if new evidence supports a change:

- Variation of the interval between mifepristone and misoprostol (evidence supports this being 1-3 days)
- Variation of the misoprostol regimen, including route of administration, specifically sublingual administration
- Substitution of gemeprost for misoprostol in accordance with RCOG guidelines and approved UK regimens

[redacted] has procedures in place to ensure that informed consent is obtained and to support delivery of care, provision of information and appropriate follow up.

Failed medical abortion

As with failed surgical abortion, if medical abortion fails, there needs to be clinical discussion about how best to proceed to complete the termination. Options might include a further course of mifepristone and misoprostol, surgical abortion, intrauterine injection with a range of agents or even hysterotomy, depending on the particular clinical circumstances.

Monitoring and reporting

Audit will be undertaken of all cases where treatment with mifepristone is used, including recording of dosage regimens, outcomes, adverse events and follow up. Reports will be made six monthly to the [redacted]. Suspected adverse events will be reported to the TGA, the sponsor and the Ethics committee.

Revisions to practice, information and consent forms

New evidence may lead to changes in treatment regimens. Any necessary changes will be reviewed and approved prospectively by the treating doctor and notified to the Ethics committee.

[redacted]

[redacted] Metadata & Endorsement/ Publishing Request Form

Network / BRG Name: [redacted]		Cost Code
Prepared by: [redacted]	Department: [redacted]	
Phone: [redacted]	Page No.: [redacted]	e-mail: [redacted]
Has this document been approved by your Director/Manager	Yes ☒	No ☐
Committee(s) this document has been endorsed by (list if appropriate): [redacted]		

Does this replace an existing document?	**No**
If yes, name of existing document	

Endorsement as outlined in Document Endorsement, Notification & Publication Policy.

I approve the above document and request it be published on the [redacted] Intranet.

[redacted]

Executive Director (Tier 2)

20 February 2008

Date

For all documents

Chair, Area Executive Directors Meeting (AEDM)

Date

For policies only

Following endorsement, this form (with the TRIM number) and an electronic copy of the policy is to be forwarded to the [redacted] Web Information and Development Services.

[redacted]

[redacted]

Midtrimester Termination of Pregnancy

Using Mifepristone and Misoprostol

[redacted]

Version 1.1

Devised: February 2008

For Implementation: Friday 16 May 2008

[redacted]

PURPOSE

This Procedure describes the process to be followed when conducting medical termination of pregnancy using **mifepristone and misoprostol** between 13 – 28 weeks for fetal abnormality, maternal illness or death in utero (FDIU). It can also be used for extremely premature prelabour rupture of the membranes (PPROM).

This Procedure does not cover the legal / counselling aspects of pregnancy termination which are already comprehensively addressed in [redacted] *Procedure For The Management Of A Woman Undergoing Termination Of Pregnancy.*

SPECIAL CASES

Pregnancies with a **uterine scar** must be discussed with the responsible consultant as care may need to be individualised.

Misoprostol is not to be used in the **third trimester.** In addition, second trimester pregnancies with a **fetal size greater than 28-30 weeks** must be discussed with the responsible consultant as the most appropriate induction method or dose may vary from that described here.

CONSENT PROCESS

- Appropriate counselling and legal requirements must be met as per *Procedure For The Management Of A Woman Undergoing Termination Of Pregnancy.*
- At the time of booking the procedure (i.e. prior to admission), the consultant or registrar caring for the woman must:-
    - **Carefully explain (using an interpreter where necessary)** the information contained in the Consent for Medical Midtrimester Termination of Pregnancy using Mifepristone and Misoprostol in particular noting
        - The special prescribing information regarding mifepristone and misoprostol
        - The possible complications and side-effects of the termination process
        - That the woman and her family should be certain about her decision before commencing the process. Should she change her mind about termination after the mifepristone is given, serious injury to the fetus is possible
    - **Prescribe** Mifepristone 200mg PO on an outpatient prescription (for inpatients or when outpatient pharmacy is closed, see next section)
    - **Instruct** the patient to take the Mifepristone at about 9pm, just under 36 hours prior to her admission to hospital for misoprostol (NOTE: new research is suggesting a shorter mifepristone-misoprostol interval may work just as well – even down to 8 hours - so consultants have discretion here but the bulk of studies have involved a 24-36 hour interval). Mifepristone should be taken at least TWO hours after eating and the woman should not eat for a further TWO hours after taking it.
    - **Ensure** that the:
        - **White** copy of the signed Consent is carefully filed in the medical record
        - **Pink** copy of the signed Consent is taken by patient to the outpatients pharmacy with her prescription.
        - **Information Section** of the Consent papers is given to the woman to take **home.**

PROCEDURE

- All midtrimester terminations of pregnancy must be overseen by an obstetric consultant
- Only in exceptional circumstances should women undergo a midtrimester termination of pregnancy and surgical sterilisation during the same admission. The responsible consultant must personally review such women.
- Mifepristone is contraindicated in women with chronic adrenal failure.
- Women with bleeding disorders or taking warfarin need careful review before termination.
- Medical termination of pregnancy will occur in two stages
    - Mifepristone 200mg PO x 1 tablet taken **at home** at approximately 9 pm (taken 2 or more hours after food with no further eating for another 2 hours i.e. empty stomach).
    - Misoprostol given vaginally and orally as per the protocol below. Misoprostol is to be administered **in hospital** commencing in the morning approximately 36 hours (this may change to 24 hours or less depending on new research) after the mifepristone was taken i.e.admission by 0600 and first dosage by 0700 where possible, with first dose ideally administered by the night registrar not the day team.

[redacted]

- Prescribing, Dispensing And Storing Mifepristone:
  - Mifepristone 200mg PO tablet x 1 is to be prescribed ONLY by a TGA-authorized prescriber.
  - It is to be dispensed by the Clinic (Outpatient) Pharmacy with the woman instructed to take it at home as above.
  - In the event that the Pharmacy is closed and the woman is currently a patient within the hospital, the following procedure will take place:
    - At the discretion of the medical officer (authorized TGA prescriber) the mifepristone will either be
      - Written on an inpatient chart whereby a member of the nursing staff will administer the dose to the patient
      - Written on an individual discharge or outpatient script and the on-call pharmacist will dispense the prescription
    - To safeguard the accountability of the mifepristone, the drug will be stored in a locked safe in the antenatal ward, separate from other drugs, and made accountable. A separate drug register will be used for this purpose.
  - Should a second dose of mifepristone be required (see below) the patient will remain an inpatient and the dose prescribed on an inpatient chart and administered by a member of the nursing staff.
- Admission Practice
  - A bed must be pre-booked on the antenatal ward via [redacted]
  - **A Recommendation For Admission Form** must completed by the doctor arranging the procedure. The form must be taken by the woman to the admissions desk in the hospital foyer on or before the day of admission i.e. before she goes up to the antenatal ward.
  - Whenever possible, the woman is to be admitted to the antenatal ward on Monday to Friday at 0600 hours so that the first dose of misoprostol may be administered by the **night registrar** at 0700 hours
  - FBC / group & hold are to be collected on admission.
- The following medications are to be charted on admission (CHECK FOR PATIENT ALLERGIES):-
  - Misoprostol (see next section)
  - Diclofenac 50mg PO tds prn. NOTE: Analgesia should be given liberally. See Educ Notes
  - Metoclopramide 10 mg IV / IM q4h prn
  - Morphine 5 – 10 mg SC q3h prn
  - Cabergoline 1 mg stat PO is to be offered after deliveries > 18 weeks as per *Procedure For Lactation Suppression Using Cabergoline*. Patient Information Sheet should be given.
  - RhD Ig 625IU IM if woman Rh negative
  - Anxiolytic such as Lorazepam 1 – 2 mg q6h prn
- Misoprostol is to be charted on admission as:-
  - Misoprostol 800 microgram (4 tablets) VAGINALLY followed 3 hours later by
  - Misoprostol 400 microgram * (2 tablets) ORALLY every 3 hours to a maximum of four oral doses.
    - *Women with an FDIU fetus > **20 weeks** in the presence of a **uterine scar** should receive 200 microgram (1 tablet) rather than 400 microgram.
    - This misoprostol regimen is taken from RCOG 2004 Guideline, with the lower dose for FDIU and scarred uterus being adapted from the previous [redacted] Hospital Procedure.
    - Oral misoprostol should ideally be given with food but this may not always be possible.
  - 97% of women will deliver with this regimen, most within 15 hours.
  - **Undelivered** women (2 - 3%) must be reviewed by a registrar or consultant after which the following will generally be prescribed:
    - Mifepristone 200mgPO to be given at midnight (timing will need to be adjusted appropriately if the first misoprostol dose was given later than 8am) followed the next morning by
    - Misoprostol 800 microgram (4 tablets) VAGINALLY followed 3 hours later by
    - Misoprostol 400 microgram * (2 tablets) VAGINALLY every 3 hours to a maximum of five total vaginal doses including the 800 microgram dose.
      *200 microgram (1 tablet) for FDIU > 20weeks with uterine scar.
  - Women **still undelivered** after this second course (about 0.3%) must be reviewed by a consultant. Subsequent management options include:
    - Repeating above regimen
    - Extra-amniotic PGF2a
    - ARM and syntocinon
    - Surgical evacuation of the uterus
- The first dose of misoprostol (800 microgram vaginally) is to be administered by a registrar, ideally the night registrar at about 0700 am on a normal working day. The subsequent oral doses are to be administered by the midwifery/nursing staff.
- The woman is to remain on the bed for 30 minutes after any vaginal dose.
- Dosing can continue after the membranes rupture if delivery is not imminent.

[redacted]

- Observations to be performed:-
  - BP, pulse and temperature on admission and thereafter fourth-hourly unless required more frequently by the clinical situation. Once labour is established, observations are to be recorded hourly.
  - A fluid-balance chart is usually not required. However, one should be used in women who are at risk of dehydration such as those:
    - Having significant vomiting and diarrhoea
    - Who have not delivered in the first 24 hours and whose oral intake is limited
    - Having extra-amniotic PGF2a
- Diet:-
  - Clear fluids after onset of contractions (full diet until then)
  - Fast once membranes have ruptured and remain fasting until placenta delivered and declared complete

RETAINED PLACENTA / PLACENTAL FRAGMENTS

- This will occur in one-third to one-half of cases.
- If the placenta is not expelled within 30 minutes of delivery of the fetus (earlier if bleeding is excessive), assisted removal is indicated. Recent studies show that the placenta is frequently in or just above the cervix where it can easily be removed using a bivalve speculum and sponge forceps in the Procedure Room on the antenatal ward (Tang 2001). If this is not successful the woman will need to go to the operating theatre for evacuation of the uterus.
- Oxytocin may be infused while awaiting transfer to the operating theatre. Commence at 40units in a 1000mL flask of Hartmanns run at 250 mL per hour.
- A prophylactic dose of cefazolin 1g stat intravenously (or clindamycin 600mg IV for *immediate penicillin sensitive* patients) should be administered if either sponge forceps or manual removal of placenta is undertaken.

LACTATION SUPPRESSION WITH CABERGOLINE 1mg stat

- Cabergoline 1mg as a single oral dose, taken with food, is routinely offered for lactation suppression in gestations terminated at 18 weeks or greater (see Lactation Suppression With Cabergoline Procedure)

PAPERWORK AND BURIAL/CREMATION REQUIRMENTS

- These must be attended as per existing Procedures for the management of stillbirths, neonatal deaths and fetal anomalies.

POSSIBLE COMPLICATIONS AND SIDE-EFFECTS FROM TERMINATION PROCESS

- Rare but serious complications of labour and delivery can occur in the midtrimester **as they do at term** and the woman must be informed about them.
- Overall in Western countries 1 per 10,000 women die in pregnancy or childbirth.
- The most serious complications of labour and birth, whether at term or in the midtrimester, include:
  - Haemorrhage heavy enough to require blood transfusion: **10 - 20 per 1000**
  - Unplanned major abdominal surgery because of heavy bleeding or rupture of the uterus or problems with the placenta: **5 per 1000**
  - Unplanned emergency hysterectomy for the above problems: **1-2 per 1000**
  - In addition there is a **1 per 100,000** risk of fatal infection from clostridium sordellii, a bowel commensal, that appears to be related to the use of mifepristone
- The lesser side-effects of the medications are:
  - Mifepristone
    - Nausea and vomiting 15 – 20%
    - Headache 15 - 20%
    - Occasional pelvic cramping before admission
  - Misoprostol
    - Fever > 37.5 degrees 50%
    - Nausea and vomiting 25-50%
    - Diarrhoea 5%

  NOTE: The incidence of misoprostol side effects is related to the number of doses given. When pre-treatment with mifepristone is utilised, significantly fewer doses of misoprostol are needed.

[redacted]

EDUCATIONAL NOTES

- **Mifepristone** is a reversible synthetic progesterone receptor blocker first synthesized from norethisterone in 1980. It also has anti-glucocorticoid action.
- Progesterone keeps the uterine muscle quiet during pregnancy by inhibiting the production and action of prostaglandins. Reversal of the dominant influence of progesterone is the key to initiating labour. Blocking the progesterone receptor with mifepristone increases the synthesis of natural prostaglandins five-fold (Swahn 1988). In addition it potentiates the action of administered prostaglandins. Original research suggested that a 24-36 hour pause between mifepristone and prostaglandins was necessary to optimize the effect but more recent research suggests that such a time delay might not be necessary (Creinin 2004).
- Other medical uses of mifepristone:
    - O&G:
        - Infertility
        - Contraception – emergency and longterm
        - Fibroids and Endometriosis
        - Breast Cancer
    - Non-O&G
        - Brain tumours such as meningiomas
        - Cushing's Syndrome
- Mifepristone has been used for first and second trimester pregnancy termination by many millions of women around the world. It was licensed in France in 1988 and subsequently in other countries including UK, USA and New Zealand. As there is not yet a drug company supplying the medication in Australia, mifepristone is listed by the Therapeutic Goods Administration as an unapproved product. It is expected that a supplier will shortly become available. Until then we will be importing the medication from overseas. Each prescriber requires individual TGA approval.
- Many large studies using prostaglandins (PG) alone or in conjunction with mifepristone have shown the following benefits of mifepristone in second trimester termination:

	Mifepristone + PG	PG Alone
Median Delivery Time	7 hours	16 hours
Median PG Doses	3	5
Undelivered 24 hours	2%	20%
Undelivered 48 hours	0.3%	10%

- In addition, the shorter delivery time and reduced number of PG doses reduces the **pain** of the procedure without being associated with any increase in risks.
- There is no evidence misoprostol alone has any advantages over the combination of mifepristone and misoprostol.
- Mifepristone side-effects are minor (see page 2) but might increase with the time delay before misoprostol is given. If more research validates this finding, the interval between the two could reduce from the current 24-36 hours down to 8 hours or less.
- While the recommended dose for mifepristone was initially 600mg (3 tablets), a number of trials have demonstrated that 200mg (1 tablet) has equivalent efficacy (Webster 1996).
- Mifepristone is contraindicated in women with chronic adrenal failure. In addition, women with bleeding disorders or taking warfarin need careful review before commencing termination.

- **Misoprostol** is a synthetic prostaglandin E1 analogue
- Compared to the other widely-used PG E1 analogue, gemeprost (Cervagem), misoprostol has
    - equivalent efficacy
    - a similar rate of side-effects (misoprostol more fever, gemeprost more GI upset).
- However misoprostol has a number of advantages over gemeprost:
    - can be given by mouth
    - about 100 x cheaper
    - stable at room temperature. Unlike gemeprost, it therefore does not need to be
        - Kept frozen
        - Thawed for 30 minutes before usage
        - Used soon after thawing because of rapid deterioration in efficacy after 40 minutes at room temperature

[redacted]

- Vaginal misoprostol is more effective and has fewer side-effects than oral misoprostol but women prefer the oral route. The Aberdeen Group, whose published administration regimen we have adopted, has found that one large vaginal dose gives sufficient direct cervical effect that subsequent smaller doses can be given orally without loss of efficacy (El-Rafaey 1995). Their median delivery time with this regimen is 5.5 hours where there has been a previous live birth and 6.8 hours where there has not (Ashok 2004)
- Misoprostol is contraindicated in women with allergy to other prostaglandins.
- Misoprostol is not a bronchoconstrictor and is not contraindicated in asthmatic women.

- **Managing Pain**
  - It is important to minimize the woman's pain as much as possible.
  - Pain is increased by
    - Nulliparity
    - Increasing gestation
    - Duration of process
    - Number of prostaglandin doses required (Hamoda 2004, Ashok 2004)
  - Pain is reduced by
    - Pre-treatment with mifepristone
    - Liberal use of NSAIDs
      - Women given **diclofenac 100mg** at the commencement of the induction required significantly less morphine than women given paracetemol 1000mg and dihydrocodeine 20mg (Fiala 2005).
      - NSAIDs interrupt the synthesis of natural PGs. They do not reduce the efficacy of administered PGs and do not prolong the labour process.

- **Complications** / risks of midtrimester medical termination of pregnancy using mifepristone and misoprostol are approximately:

Retained placenta	30%
Live Birth	8%
Infection	2%
Haemorrhage requiring blood transfusion	1%
Uterine rupture	0.5%
Undelivered at 48 hours	0.3%
Death	0.002%

- **Retained placenta** rates are inversely proportional to gestation, being about 35% before 20 weeks and 12% after 20 weeks when large numbers of studies are averaged. However, several major reports have now shown that in most cases the placenta is in or just above the cervix and can be managed on the ward using a speculum and sponge forceps rather than transferring the woman to theatre. The highly respected Edinburgh group has reduced the need for evacuation of POC in OT from 33% in 1993 to 11% in 2001 by making this adjustment. (Thong 1993; Tang 2001) The Aberdeen group has reduced its rate to 7%. Vindicating that this approach seldom leaves placental tissue behind, the rate of curettage for RPOC after discharge in Aberdeen is only 0.7% (Ashok 2004).

- **Live birth** is seldom mentioned in reports and where it is, the agents used were not mifepristone/misoprostol. Available data suggests the rate is about 5-10% (Stroh 1976, Owen 1996). Beyond 22 weeks it is common to instill agents into the amniotic sac or fetal heart prior to IOL in order to prevent this occurrence. At earlier gestations, parents should be warned of the possibility of a pre-viable infant being alive for a short time. Staff need to provide comfort and support to both the infant and the parents.

- **Infection** rates are difficult to ascertain since infection is often a presumptive diagnosis given, for example, to heavy or prolonged bleeding in the absence of other features such as fever or tenderness. It is a diagnosis far more often allocated in the UK than other countries (Shannon 2004). The rate is <1% for all medical termination and is probably 1- 2% for cases in the second trimester. Special mention must be made of very rare (1 per 100,000) deaths from clostridium sordellii toxic shock apparently attributable to mifepristone. It is thought that the drug's antiglucocorticoid and anti-

[redacted]

cytokine actions might be responsible. The symptoms and signs are very subtle and practitioners must be alert to the possible diagnosis in the unwell woman after termination.

- **Haemorrhage** requiring blood transfusion occurred in 0.1% (1 out of 956) women in the Edinburgh study (Tang 2001) and 0.7% (7 out of 999) women in the Aberdeen study (Ashok 2004). This is little different from typical rates of blood transfusion at term. A low-lying placenta in one study was associated with significant haemorrhage in a single patient (Thong 1992); however it is rarely reported. Placenta accreta can result in hysterectomy as it can at term (Dickinson 2002). It should be especially anticipated in women with a low-lying placenta and previous caesarean births.

- **Uterine rupture** is an uncommon event mostly occurring in women with a previous caesarean birth. However, it is also more common with grand multiparity, increasing size of the uterus, number of prostaglandin doses given and the use of oxytocin. Women with prolonged labours must be watched closely and great care must be taken with the use of oxytocin. In the Edinburgh study the hysterectomy rate for uterine rupture was 0.1% (1 out of 956) while in the Aberdeen study of 999 women, no hysterectomies occurred. Reasonable figures for counselling patients are a risk of rupture of less than 0.5%, broken down to 1% in women with previous CS and 0.2% in women without a scar on their uterus (Norman 1995, Chapman 1996, Ashok 2004, Dickinson 2005). A few of these women will require hysterectomy while in the majority the tear will be repairable. The risk of uterine rupture is not reduced by using mifepristone. While it significantly reduces the number of prostaglandin doses required, it also sensitizes the uterus to the prostaglandin.

Abbreviations

ARM	Artificial Rupture Of Membranes
BP	Blood Pressure
FDIU	Fetal Death In Utero
GI	Gastrointestinal
IM	Intramuscular
IOL	Induction Of Labour
IV	Intravenous
KCL	Potassium Chloride
NSAIDs	Non-steroidal anti-inflammatory drugs
O&G	Obstetrics and Gynaecology
OT	Operating Theatre
PG	Prostaglandins
PGF2a	Prostaglandin F 2a
PO	Per Oral (by mouth)
POC	Products of Conception
PPROM	Preterm Prelabour Rupture of the Membranes
RCOG	Royal College Of Obstetricians and Gynaecologists
RPOC	Retained Products of Conception
SC	Subcutaneous
[redacted]	[redacted]
TGA	Therapeutic Goods Administration
TOP	Termination of Pregnancy

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[redacted]

APPENDIX 1 : [redacted]

[redacted] Patient Information Sheet and Consent

Medical termination of pregnancy in the second trimester (13 – 28 weeks) using oral mifepristone prior to vaginal and oral misoprostol

What is mifepristone?

Mifepristone is a man-made hormone, similar in structure to the natural female hormone, progesterone. Because of the similarity, mifepristone can block the actions of progesterone. Since progesterone keeps the uterine muscles relaxed and the pregnancy going, mifepristone acts to prepare the uterus to contract and begin the labour process.

Mifepristone has been licensed for pregnancy termination in France since 1988, the UK since 1990, USA since 2000 and NZ since 2001. In 2006 it became licensed in Australia but at the moment its use is restricted to individual doctors who must be approved by the government body known as The Therapeutic Goods Administration (TGA).

Mifepristone is available as a 200mg tablet. You take it by mouth at home some hours (currently 24-36 hours, but shorter times may be just as effective) before you come into hospital.

Your consent is required to receive this medication.

What is misoprostol?

Misoprostol is a man-made prostaglandin, similar to naturally occurring substances found in most body cells. Its most common use is to prevent stomach ulcers in patients taking arthritis medication. However, it is also very effective in making the uterus contract. As a result, misoprostol and other man-made prostaglandins have been used to induce labour and reduce bleeding after childbirth for many years. They are also used for termination of pregnancy.

Misoprostol is a very safe medication, even if taken every day for years to prevent stomach ulcers. Despite this, the manufacturer has said that it will never seek to have misoprostol licensed for use in pregnant women. This is not unusual. Many medicine manufacturers don't want the responsibility of having their medications used by pregnant women, even when shown to be safe. Such medications can still be prescribed by doctors but are said to be 'off license' in usage.

Misoprostol is approved for termination of pregnancy by the Colleges of Obstetricians in Australia, New Zealand, the United States and the United Kingdom among many others. Misoprostol has been approved by the [redacted] Drug Committee for pregnancy termination at [redacted] Hospital for a number of years.

Misoprostol is a tablet. It is administered in hospital, generally at around 8am. The first dose (4 tablets of 200 micrograms i.e. 800 micrograms total) is inserted into your vagina. The next doses (2 tablets of 200 micrograms i.e. 400 micrograms total) are given by mouth every three hours up to a maximum of four doses by mouth.

Your consent is required to receive this medication.

Extremely Important Note

Should a woman decide to continue with her pregnancy **after** taking mifepristone (with or without misoprostol) there is a high possibility of giving birth to a baby with abnormalities or other evidence of damage. So you need to be certain of your decision from the start.

[redacted]

What is the benefit to you of taking mifepristone some hours before misoprostol?
Taking a mifepristone tablet by mouth some hours prior to misoprostol makes the labour process faster and less painful for you.

	Mifepristone + Misoprostol	Misoprostol Alone
Average Time in Labour	7 hours	16 hours
Usual number of misoprostol doses needed	3	5
Still not delivered after 24 hours in labour	2% of women	20% of women
Still not delivered after 48 hours in labour	0.3% of women	10% of women

About 97-98 % of women will deliver with the first course of mifepristone / misoprostol i.e. within 15 hours. Those who are not delivered or nearly delivered by midnight (timing may be adjusted if the first misoprostol dose is given later than 8am) will have a further course of treatment consisting of:

- Another tablet of mifepristone 200mg by mouth at midnight, followed at 8am next morning by
- Four tablets of misoprostol (800mcg) put into the vagina followed after 3 hours by
- Two tablets of misoprostol (400mcg) put into the vagina and repeated every 3 hours up to a total of five vaginal doses including the initial 800mcg dose

How Safe Is Termination Using Mifepristone and Misoprostol?
Mifepristone and misoprostol are the most commonly used medications for termination of pregnancy around the world. They have been taken by hundreds of thousands of women and their safety is well established. However, when discussing safety it is important to remember that just being pregnant and giving birth carries a small risk. Deaths of women from pregnancy and giving birth (including miscarriage) occur at a rate of 1 death per 10,000 pregnancies in the developed world. There is little difference in risk to you between giving birth at full term or having a termination in the middle of pregnancy.

Serious complications of labour and delivery whether at full term or in the middle of pregnancy include

- Bleeding heavy enough to require blood transfusion (about 10 -20 women per 1000)
- Unplanned major abdominal surgery because of heavy bleeding or problems with the placenta or tearing of the uterus (about 5 women per 1000).
- Loss of the uterus (hysterectomy) as a result of this is (about 1 - 2 women per 1000)
- Death due to infection with clostridium sordellii occurs in about 1 per 100,000 women when mifepristone is used. Clostridium sordellii is a bacterium which lives in our bowels. It is usually completely harmless but can occasionally make us very sick.

Less serious complications of termination in the middle of pregnancy:

- Sometimes all or part of the placenta (afterbirth) does not come away at the time of birth. This happens about 35% of the time before 20 weeks and 12% after 20 weeks. Usually, a brief general anaesthetic in the operating theatre to remove the placenta is required.
- Low-level infection requiring antibiotics occurs in a small percentage of women.
- Occasionally the baby is alive for a short while after birth. Staff will provide it with warmth and comfort. Depending on how far along your pregnancy is, the treating doctor will sometimes recommend measures prior to termination to avoid this happening.

Side effects of mifepristone:

- Vomiting and/or headache can each occur in 15-20% of women.
- A small percentage of women will also get period-like cramping.
- Medications are available to manage these side-effects

Side effects of misoprostol:

- Vomiting, diarrhoea and fever each occur in 25 -50% of patients.
- All women will have cramping from the labour process.
- Medications are available to manage these side-effects

[redacted]

[redacted]

Consent For

Medical Midtrimester Termination Of Pregnancy
Using Mifepristone and Misoprostol

I _____ (insert patient name) acknowledge that I have received a copy of the Patient Information Sheet and Consent concerning medical midtrimester termination of pregnancy using mifepristone and misoprostol. I acknowledge that I have read the document or had read to me, and that I have understood it.

In addition I have had the risks of the procedure explained and my questions answered to my satisfaction by Dr _____(insert name of medical officer).

I acknowledge that if I change my mind about termination after the medications have been commenced, serious complications to my baby could result.

I agree to termination of pregnancy utilising oral mifepristone and oral and vaginal misoprostol. I acknowledge that both medications to be used in my pregnancy termination, while considered the best available, have restrictions:

Mifepristone (Brand name: Mifegyne ®, Exelgyn) is not yet supplied in Australia by a drug company and is therefore considered an 'unapproved' medication at the moment. It is however approved for use in [redacted] by prescribers who have obtained authorization from the Australian Government Therapeutic Goods Administration. I acknowledge that it is an approved medication for pregnancy termination in many countries and is considered safe and effective.

Misoprostol (Cytotec ®, Searle) is not licensed for use in pregnancy (manufacturer's commercial decision) but has been used by many millions of pregnant women around the world to induce labour both at term and in the second trimester. It is approved for pregnancy termination by the [redacted].

_____ Patient Name

_____ DOB

_____ Address

_____ Patient Signature

_____ Medical Officer Name

_____ Medical Officer Signature

_____ Witness Name

_____ Witness signature

Attachment 2-

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MIFEPRISTONE

for the Management of Pregnancy Loss and Medical Termination of Pregnancy at the

[redacted]

Application for Authorised Prescribers: Access to unapproved therapeutic goods

[redacted]

Total number of Pages = 8

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1) INDICATION FOR THE USE OF MIFEPRISTONE

For the Management of Pregnancy Loss and Medical Termination of Pregnancy at [redacted]

We are applying for the access to Mifepristone for the management of pregnancy loss and the medical termination of pregnancy at [redacted]

The use of Mifepristone for the management of pregnancy loss will include any fetal death in utero in the 2nd and 3rd trimester. Mifepristone will be used to prime the cervix prior to the commencement of the induction of labour. Early pregnancy loss (includes missed and silent miscarriages only) in the 1st trimester will also be managed with mifepristone and misoprostol to improve the current efficiency of our current medical management regime (misoprostol alone).

The use of Mifepristone for the medical termination of pregnancy will include termination deemed appropriate by the Maternal Fetal Medicine multidisciplinary team (involving at least two MFM consultants, psychiatry, social worker, neonatologists and midwifery with often involvement of the ethics committee) for three main indications as follows. Firstly, serious fetal anomalies and genetic syndromes such as trisomy 18/21/13. Secondly, pregnancies with poor prognosis including very preterm, prolonged rupture of membranes and severe early onset intrauterine growth restriction. Lastly, for medical disorders in pregnancy such as severe cardiac disease that may threaten the life or worsen the prognosis for the mother.

Mifepristone will NOT be used for non-medical or social reasons for the termination of pregnancy and will NOT be affiliated with or used in any community abortion clinics in [redacted] or surrounding areas.

The specific clinical indications for the use of Mifepristone include:

a) Early pregnancy loss with an intact gestational sac including missed and silent miscarriages and excluding incomplete miscarriages
b) Management of fetal anomalies in the first trimester
c) Management of fetal anomalies in the second trimester (over 16 weeks)
d) Induction of labour for fetal death in utero in the 2nd and 3rd trimester

2) CLINICAL JUSTIFICATION

Seriousness of condition

The management of pregnancy loss is a very emotional and traumatic time for women and their families.

The current protocol for [redacted] incorporates misoprostol alone (400mcg-600mcg; 4 to 6 hourly, per orally or vaginally), which can take between 24 and 48 hours for some women. We have had one distressing case this year that took over 3 days and was associated with frustration and distress for the woman, her family and the staff of the maternity unit. This contributes to considerable psychological stress for the woman and midwifery staff cating for them. The procedure will involve 3 or more nursing shift changes along with the requirement to be in Delivery suite over that time with the distress of hearing other women labouring and babies crying.

There is a need to improve our management of pregnancy loss and medical termination of pregnancy through the use of mifepristone in conjunction with misoprostol. There is strong evidence that the use of mifepristone will improve the efficacy and shorten the duration of the labour along with reducing psychological stress for women, their families and the staff involved in their care.

Justification for the use of the unapproved product

There are clear advantages in the literature when using the combination of Mifepristone and Misoprostol including improved efficacy, satisfaction and positive experiences from the international community and more recently in New Zealand (WHO 2003; RCOG 2003).

There is widespread international evidence from the World Health Organisation (WHO) and systematic reviews from the Royal College of Obstetricians and Gynaecologists (RCOG) have shown that the combination of mifepristone followed by misoprostol is the most effective and safe way for the induction of labour in 1st and 2nd trimesters. Evidence has shown that mifepristone results in the successful expulsion of the products of conception for 95% of women, up to 9 weeks gestation (RANZCOG, 2009).

In the UK, the national guidelines state that 'single agent regimens are not considered to have a role where mifepristone is readily available, and are not considered further in this guideline' (RCOG, 2003). A review article by Vargas and Diedrich in 2009 showed that misoprostol only protocols reported more side effects, required higher doses with an increase in the duration when compared to mifepristone-misoprostol combinations.

A Cochrane review by Kulier and associates in 2004 showed that mifepristone alone is less effective when compared to the combined regimen mifepristone/misoprostol (RR 3.76 [2.30 to 6.15]). There were five trials comparing misoprostol alone to the combination of mifepristone and misoprostol. Four trials showed higher effectiveness with the combined regimen with the reported relative risk of failure with misoprostol alone ranging between 1.4 to 3.8.

A Western Australian study by Dickinson and colleagues in 2010 studied the use of mifepristone and misoprostol for second trimester terminations for fetal anomalies. This cohort study of 388 women showed there was a significant reduction in the duration of

abortion (8.6 hrs versus 15.5 hrs) and hospitalisation (27.2 hrs versus 31.5 hrs) with combined therapy versus misoprostol only. Complications such as fever, blood loss and the requirement for a blood transfusion was reduced in the Mifepristone and Misoprostol group compared with the misoprostol alone, although this was not statistically significant.

A randomised controlled trial of 64 women undergoing 2nd trimester termination of pregnancy by Kapp and associates found the median duration of the labour was reduced in the Mifepristone group (10 hours) compared with the misoprostol alone group (18 hours). There was reduction in the number of placental retention (3.1% compared with 6.3%, p = 0.61), length of hospitialisation and analgesic requirements comparing Mifepristone to Misoprostol alone. The rate of side effects reported was similar across the two groups.

There is obvious economic benefit to the combination of mifepristone and misoprostol in the management of pregnancy loss and medical termination of pregnancy. The minimum cost of one delivery suite bed per day is approximately $1,000 and the maximum cost is $2549 per bed per day. Mifepristone could significantly reduce the cost by reducing the length of stay in hospital (from 2 days to one day) and length of time requiring a delivery suite bed (which relates to a cost saving between $500-1000 for each woman).

Most importantly, the efficiency of the medication in achieving successful expulsion of the products of conception will result in less psychological stress and frustration for the woman and her family.

3) EFFICACY AND SAFETY DATA

There was a large population study in the United States developed to assess the safety and efficacy of mifepristone from the largest provider, the Planned Parenthood Federation of America. Between 2001 and 2004, 95163 mifepristone abortions were provided to women. Heavy bleeding was the most common complication, occurring at the rate of 2.2 per 1000 women (95% CI 1.9 –2.5). There was one death reported in this period from septic shock [1.1 per 100,000 (95% CI 0.3 –5.9)].

Side effects (Liverpool Women's NHS Foundation Trust 2008, product information and Iyengar et al., 2008)

Common side effects for mifepristone include:

- Bronchoconstriction, worsened if the woman had recently smoked a cigarette prior to ingestion
- Cramping (light to moderate)
- Nausea, vomiting and diarrhoea
- Infection following abortion (<5%)

Uncommon side effects include hypotension (0.25%), septic shock (*Clostridium sordellii* endometritis), skin rashes (0.2%), headaches, malaise and vagal symptoms (hot flushes, dizziness and chills).

4) PRODUCT DETAILS

Generic name is Mifepristone
Trade name is Mifegyne® and is also known as RU 486
Supplier – Exelgyn (in France – this is the company that New Zealand use) or Danco Laboratories (in United States of America)

5) ADMINISTRATION AND MONITORING PROTOCOL

Dosage: 200mg orally, 36-48 hours prior to the commencement of the pregnancy loss procedure.
Route of administration: ORALLY
Duration of treatment: ONCE ONLY and then misoprostol administration as per the following the table

Details of Administration and Monitoring
Each woman is given written information and consent for both Mifepristone and Misoprostol to be signed prior to commencement. Mifepristone needs to be administered orally on licensed premises and dispensed from the hospital pharmacy by individual prescription. The patient should be observed taking medication and should remain on the ward for one hour after ingestion. The couple can then return home.

Arrangements should be made for the couple to return 36-48 hours after ingestion for the next stage of the induction.

After 48 hours, the couple returns to Delivery Suite. The first dose of misoprostol is administered per vaginally. WHO recommends 800mcg per vaginally for the first dose. There are corrected doses of misoprostol dependent on gestation, previous uterine scar and on whether the induction is for fetal abnormality or intrauterine fetal death.

Table 1: Misoprostol Dosage Regimens when used in Conjunction with Mifepristone *(Adapted from* [redacted]

	No Uterine Scar	Previous scar
Intrauterine Death		
13-17^{+6} weeks	200mcg PV/6 hourly 4 doses then review	100mcg/6 hourly 4 doses then review
18-25^{+6} weeks	100mcg PV/6 hourly	50mcg PV/6 hourly
26 weeks onwards	50mcg PV/6 hourly	25mcg PV/6 hourly
Fetal Malformation		
< 24 weeks	800mcg PV then 400mcg PO 3 hourly 4 doses then review	400mcg PV then 200mcg PO 3 hourly 4 doses then review
24-31^{+6} weeks	400mcg PV then 200mcg PO 3 hourly 4 doses then review	200mcg PV then 100mcg PO 3 hourly 4 doses then review
32 weeks onwards	50mcg PV/ 6 hourly 4 doses then review	25mcg PV/ 6 hourly 4 doses then review

Procedures prior to Discharge

- Discussion about possible causes, investigations and follow up
- Emotional support with the assistance of Social work
- Inform local or community GP
- Ensure a follow up appointment is made prior to discharge with the Consultant Obstetrician caring for this woman
- Organise additional follow up as required (geneticist, paediattician, maternal-fetal medicine follow up, social work etc)
- Suppression of lactation with Dostinex (Cabergoline, 1mg stat dose, orally)
- Ensure Anti D is given if Rhesus negative and Rubella status is checked prior to discharge

Follow up care

Upon discharge, the woman will be given written instructions about what to expect, arrangements for follow up, accessing advice on a 24-hour basis or help in an emergency. If Rhesus negative, anti-D should be given within 72 hours of the termination.

Follow up arrangements will encompass

- A clinical assessment by a medical officer will be undertaken, ONE week after the termination and if required, serum βHCG or ultrasound measurements.
- Ongoing access and use of effective contraception should be addressed at the follow up visit

Reporting of Side effects

All suspected side effects from Mifepristone will be reported to the TGA via the form titled the 'Report of Suspected Adverse Reaction to Drugs and Vaccine' in the Access to unapproved therapeutic goods – Authorised prescribers guidelines (page 44). In addition, a record of all patients who underwent management with Mifepristone and their outcomes, any complications and reported side effects will be recorded by [redacted] and [redacted]

Protocol for the use of Mifepristone in 1st and 2nd trimester of pregnancy.

As per the decision of the [redacted] and [redacted] of 25 May 2009.

Indication.

To decrease length of labour induction in cases of fetal anomalies, fetal death in utero or severe maternal illness in first and mid trimester of pregnancy.

Dosage.

Single tablet 200mg Mifepristone.

Administration.

Orally, 36 hours before admission to [redacted] for Cervagem (Gemeprost) protocol.

Prescription.

A prescription for Mifepristone 200mg with complete directions for use INCLUDING THE TIME IT IS TO BE TAKEN is to be given to the patient with the instructions that they are to get it filled at the [redacted] Outpatient Pharmacy – [redacted] This prescription will be filled free of charge for the patient. The pharmacy is open 8:30am – 5:00pm Mon-Fri (closed 1-2pm for lunch)

[redacted]

1 September 2009.

Attachment 2:

[redacted]

[redacted]

Medical Abortion Protocol

The Medical Abortion Protocol

The medical abortion protocol is to be adhered to by the medical practitioners of the [redacted] who have been granted Authorised Prescriber status for Mifegyne® by the Therapeutic Goods Administration (TGA).

The protocol is to be used as an alternative to surgical termination of an intra-uterine pregnancy where medical abortion is clinically assessed as the most appropriate method for women, including when surgical abortion is not available.

Precautions and Contraindications

The generic name of Mifegyne® is Mifepristone.

The generic name of Cytotec® is Misoprostol.

Mifegyne® can only be prescribed by a medical practitioner who has gained Authorised Prescriber status from the TGA.

Mifegyne® is only available to patients who are under the direct care of the medical practitioner who is an Authorised Prescriber.

Mifegyne® is not approved for general use in Australia and is still considered experimental.

The medical practitioners need to be aware of the relative and absolute contraindications to Mifegyne® and Cytotec®.

The medical practitioner need to report any suspected adverse reactions to the TGA, [redacted] Ethics Committee and [redacted]

Regime

The regime endorsed in this Medical Abortion Protocol is consistent with the most evidence-based research.

Up to 63 days gestation- the regime only:

1. One (1) tablet of 200mg Mifegyne® taken orally under medical supervision
2. 36-48 hours later, four (4) tablets of 200mg Cytotec® taken orally or vaginally
3. If a miscarriage does not commence within six (6) hours of taking the Cytotec®, further doses of Cytotec® will be taken orally or vaginally – two (2) tablets of 200mg Cytotec®

Supporting organisational documents

There are a number of organisational / quality documents that are mandatory to the medical abortion protocol and process:

[redacted]0828	Having a Medical Abortion	patient information sheet
[redacted]0825	Medical Abortion Aftercare	patient information sheet
[redacted]0832	Medical History for a Medical Abortion	internal quality document
[redacted]0835	Medical Abortion Form	internal quality document
[redacted]0830	Patient Instructions for a Medical Abortion	patient information sheet / instructions
[redacted]0824	Consent Form for Medical Abortion	internal quality document
[redacted]0215	Patient Rights and Responsibilities	internal quality document
[redacted]0203	Customer Complaints / Feedback pamphlet	internal quality document
[redacted]0349	Privacy and Confidentiality Policy	internal quality document
[redacted]0897	Medical Record	internal quality document

[redacted]

Medical Abortion Protocol

[redacted]

Patient Admission – Patient Information Collection	Patient bookings will be made via telephone by either the patient or their referring medical practitioner. A patient requiring an interpreter service should be identified at this point. ↓ Patients will be admitted at the Front Desk [redacted] Their personal details e.g. Surname, First Name, Date of Birth, Address, Postal Address, Home Telephone Number, Mobile Telephone Number, Medicare Number, Private Health Number and Referring Doctor details will be collected onto the **Medical Record.** ↓ Patients will be shown to the bathroom and provided with instructions on to how collect a urine sample for a qualitative pregnancy test. The patient will submit the sample to the collection centre of the laboratory and then return to the Waiting Room The laboratory will process and test the sample and finally issue a Laboratory Report. Attach Laboratory Report to patient's Medical Record. ↓ Patients will be offered important literature to read whilst waiting to see a medical practitioner. Remembering some information is also available in other community languages. **Patient Information Sheet – Having a Medical Abortion** **Medical History for Medical Abortion** **Privacy and Confidentiality Policy** **Patient Rights and Responsibilities** **Complaints Management Policy** ↓ Record the **Patient Admission Session** on the **Medical Abortion Form** and ensure attached to the **Medical Record.** ↓ Patient proceeds to the **Medical Session**	"All women requesting an abortion should be offered an assessment appointment within five days of referral." (Ref 1, 2). "All women should undergo the abortion within seven days of the decision to proceed being agreed." (Ref 1,2) All information will be handled confidentially. Information from patient's record will be made available to health professionals involved in their care, but will not be released to others with patient's consent, unless legally required. All our services must comply with the relevant information and privacy legislation. Pathology sample must comply with the sample collection criteria of the laboratory i.e. labeling must include three identifiers – surname, first name and date of birth. Refer to the [redacted] Laboratory Approved Collection Manual for more information on sample collection protocols. We see a patient's health care as a co-operative and collaborative effort between patient and staff. This literature outlines the patient's rights and responsibilities i.e. what to expect from the visit and what is expected from the patient. The patient will make a valuable contribution to their care ar treatment by informing us of their medical history, answering questions about their health honestly and attending follow-up appointments etc. Patients will be made aware that are entitled to comment or complain about the treatment they receive at any time.

[redacted]

Medical Abortion Protocol

[redacted]

Medical Session – Assessment of Eligibility for Medical Abortion	All patients will be seen by a doctor to initiate the medical consultation process. The session will involve taking a comprehensive medical history and assessing eligibility of patient for medical abortion with mifepristone and misoprostol. Medical history will be recorded on the patient's **Medical Abortion Form.**	Medical assessment will include pertinent medical and obstetric history including history of allergies and all current medications. Doctor will also conduct pertinent physical examination including vital signs. Including: 1. Pregnancy test result – qualitative and quantitative 2. Ultrasound findings – CRL 3. Estimated gestational age 4. ABO Rh(D) 5. Sexually Transmitted Infections
	↓ Review completed patient form – **Medical History for Medical Abortion** – to ensure there are no absolute or relative contraindications to the Mifepristone – Misoprostol regime. Record on the **Medical Abortion Form** if the patient has / has not absolute or relative contradictions.	Mifepristone must not be prescribed if the following conditions are known or suspected: ▪ Patient's EGA is less than or equal to 63 days ▪ Chronic adrenal failure ▪ Haemorrhagic/bleeding disorder ▪ Inherited porphyria ▪ Severe anaemia ▪ Long term anticoagulant therapy e.g. warfarin, heparin ▪ Corticosteroid therapy e.g. prednisone, cortisone ▪ Allergy to mifepristone or misoprostol ▪ Irritable bowel disease or uncontrolled bowel disease e.g. severe diarrhoeae, Crohn's disease ▪ Serious systemic illness e.g. severe liver disease, heart disease, kidney failure, uncontrolled seizure disorders ▪ Serious pelvic infection (Ref 3)
	↓ Perform an unltrasound to determine CRL and confirm EGA. Document findings onto the patient's **Medical Abortion Form** including pregnancy test results and STIs.	A patient will qualify for a medical abortion with mifepristone if an Intrauterine pregnancy is identified with a yolk sac and/or embryo, and the Estimated Gestational Age (EGA) is less than or equal to 63 days, and the fetal Crown Rump Length (CRL) is less than or equal to 21mm (Ref 3).
	↓ Discuss the other critical criteria that the patient must adhere to before having a medical abortion.	A patient will qualify for a medical abortion with mifepristone if they can demonstrate that they: ✓ Able to give informed consent ✓ Be available to return to the clinic for at least 2 separate visits – last visit 10 -14 days after Misoprostol administration ✓ Live close to a hospital with emergency services and have reliable transport to get there ✓ Have a land line or mobile phone number – must be contactable 48-72 hours after taking Misoprostol ✓ Must consent to a surgical abortion if the medical abortion fails (Ref 3).
	↓ Continue Medical Session (next page)	

[redacted] [redacted]

Medical Abortion Protocol

Medical Session – Explanation of the Medical Abortion Regime

Discuss what the medical abortion regime involves and ensure patient understands the process including that Mifegyne® is not approved for general use in Australia and is still considered experimental. Explain that you are authorised to prescribe Mifegyne®.

↓

Patient proceeds to the **Counselling Session**

Step 1 - Mifegyne®

a) One (1) tablet of 200mg Mifegyne® taken orally under medical supervision
b) Patient is prepared for discharging
c) Patient to eat lightly; drink plenty of water and rest
d) One (1) tablet of 10mg Maxolon taken orally if there is nausea but no more than three (3) tablets in one (1) day
e) Wait 36 hours but no more than 48 hours before proceeding to Step 2

Step 2 – Pain relief

a) Two (2) tablets of 200mg Ibuprofen taken orally
b) Additional pain relief – take two (2) tablets of 500mg Paracetamol taken orally
c) Wait one (1) hour before proceeding to Step 3

Step 3 - Cytotec®

Select Option 1 or Option 2 but NOT both

Option 1 – at clinic:
Wet four (4) tablets of 200mg of Cytotec® with a few drops of water and place as high in the vagina as possible

Option 2 – at home:
Take four (4) tablets of 200mg of Cytotec® and place between cheeks and mouth [two tablets to each side]. Allow to dissolve slowly. Swallow any remaining reside after 30 minutes.

If a miscarriage does not commence within six (6) hours of Step 3, patient must ring clinic for more Cytotec®.

Additional Cytotec®:
Further doses of 400mg Cytotec® administered orally or vaginally as two (2) tablets of 200mg of Cytotec®

Step 4 – Assessment of the effectiveness of the regime

Part A – telephone call follow-up
48 -72 hours after Step 3 is taken, a nurse will follow-up patients to exclude infections, incomplete abortion or medication failure.

Part B – clinic appointment
10-14 days after Step 3 the patient must return to the clinic to check that the pregnancy has ended and that all tissue has been expelled from the uterus.

[redacted]

Medical Abortion Protocol

Counselling Session – Support in Decision Making	Review completed patient form **Medical History for Medical Abortion** to ensure patient meets criteria for medical abortion as an alternative to surgical abortion. Doctor should have ruled out contraindications in the medical session.	Mifepristone must not be prescribed if there are absolute or relative contraindications to the mifepristone-misoprostol regime. Refer to Medical Session – Assessment of Eligibility for Medical Abortion.
	↓ Discuss pregnancy options to ensure that the decision to have an abortion is informed, voluntary and non-coerced and the patient understands the possible effects on her of the decision she reaches.	Every woman who has an unplanned and/or unwanted pregnancy requires access to counselling which is confidential, is responsive to her social, emotional and cultural circumstances, and offers referral for available options (Ref 4).
	↓ Discuss the advantages of early medical abortion. Use the patient information sheet **Having a Medical Abortion** to guide your session. Provide information about the advantages of early surgical abortion.	Advantages of early medical abortion e.g. ▪ Non-invasive, it avoids surgical and anaesthetic risk ▪ More natural, allows privacy and control Advantages of early surgical abortion e.g. ▪ Very high success rate ▪ Procedure completed with 5-10 mins ▪ One visit to clinic
	↓ Review side effects of medical abortion. Use the patient information sheet **Having a Medical Abortion.**	Side effects of medical abortion: ▪ Bleeding ▪ Cramping ▪ Headache, nausea and vomiting
	↓ Review risks and complications of medical abortion. Use the patient information sheet **Having a Medical Abortion.**	Risks and complications of medical abortion: ▪ Excessive bleeding ▪ Infection ▪ Incomplete abortion ▪ Continuing pregnancy ▪ Ectopic pregnancy ▪ Foetal abnormalities ▪ Future fertility ▪ Other complications
	↓ Explain that the process involves at least two visits to the clinic and the importance of patient compliance with the regime.	
	↓ Provide information about the drugs used and that they are not licensed for the purpose of terminating a pregnancy in Australia.	
	↓ Discuss contraception options and provide information. Document type of contraception recommended on patient's **Medical Record.**	Use your **Counsellor Resources** Folder to supplement the information on contraception options.
	↓ Patient returns to the doctor to complete the **Medical Session**	

[redacted]

Medical Abortion Protocol

[redacted]

Medical Session – Informed Consent Process	All patients will be seen by a doctor after the Counselling Session. The purpose of this session is to facilitate the informed consent process for a medical abortion. ↓ Review the **Consent Form Medical Abortion** with the patient. ↓ Ask the patient if they have received sufficient information for the proposed treatment including the nature and probable effects and risks. ↓ Ensure patient signs the **Consent Form for Medical Abortion.** Doctor must also sign this consent form and attach to the patient's **Medical Record.** The process also needs to be recorded on the **Medical Abortion Form.** ↓	It is important that there is effective consent to medical abortion. Consent to health care must have at least three elements: ✓ It must be voluntary and freely given ✓ It must be specific ✓ It must come from a competent person (Ref 5) Checklist for giving information for patient decision-making (respecting patient's personality, beliefs, fears, values and cultural background): ▪ There should be no coercion, patients should be encouraged to be frank, ask questions and make up their own minds. Repeat information if required, and look for responses that indicate that information h not been understood. ▪ Ensure patient understands the nature of the procedure – e.g. how painful, how long it will take, how they will feel before, during and after it ▪ Ensure patient understands effects and possible risks of the procedure ▪ The availability of alternative procedures and the above information about them
	Order pathology testing – serum βHCG (first base-line), blood group and antibody screen and STI – by filling out a [redacted] **Laboratory Request Slip.** ↓ Prescribe 200mg Mifegyne® and 800 µg Cytotec® ↓ Patient proceeds to Laboratory with a [redacted] **Laboratory Request Slip** for pathology testing ↓ Patient proceeds to **Nursing Care Session**	Pre-abortion management: 1. All patients should be typed for ABO and RhD as early as possible during each pregnancy (Ref 6). It is important to identify RhD negative patients who may require the administration of prophylactic RhD-Ig. It is also important to identify patients with clinically significant alloantibodies to red cell antigens (Ref 6). 2. Monitoring of serum βHCG levels will be important in verifying the effectiveness of the abortion procedure (Ref 7) 3. Screening of lower genital tract organisms for sexually transmissible infections (STI) is important for the wellbeing of patients and has the potential for improving public health and reducing the spread of STIs in the community (Ref 8). Consult the Medical Scientists / Pathologist for specific specimen collection requirements or the Approved Collection Centre Procedures Manual for collection criteria.

[redacted]

Medical Abortion Protocol

[redacted]

Nursing Care Session – Administration of Mifegyne®	Review Laboratory Report with doctor – check RhD status, and antibody screen results. Attach Laboratory Report to patient's Medical Record and record these checks on the **Medical Abortion Form.** ↓ RhD negative patients should be provided with information about prophylactic RhD immunoglobulin to facilitate the informed consent process for the immunoglobulin. Ensure patient signs **RhD immunoglobulin Patient Information and Consent.** ↓ Review patient information sheet **Complications of Medical Abortion** with patient.	It is important that there is effective consent to prophylactic RhD immunoglobulin. Consent to health care must have at least three elements: ✓ It must be voluntary and freely given ✓ It must be specific ✓ It must come from a competent person (Ref 5) Risks and complications of medical abortion e.g. ▪ Excessive bleeding ▪ Infection ▪ Incomplete abortion ▪ Continuing pregnancy ▪ Ectopic pregnancy ▪ Foetal abnormalities ▪ Future fertility ▪ Other complications
	↓ Review patient information sheet **Medical Abortion Aftercare** with patient. ↓ Review patient information sheet **Patient Instructions for a Medical Abortion** before administrating medications. ↓ Administer the one (1) tablet of 200mg Mifegyne® and document the dosage, date and time on the **Medical Abortion Form** and the **Patient Instructions for a Medical Abortion.** Patient must remain under supervision to ensure there is no reaction to the medicine for a minimum of 30 min to 1 hour. ↓ Patient proceeds to **Nursing Care Session** – Administration of Cytotec® - Option 1 or Option 2	Important aftercare considerations e.g. ▪ DO NOT use tampons - use sanitary pads instead. ▪ DO NOT use a bath, spa or go swimming - shower or sponge down only. ▪ DO NOT have vaginal intercourse - you could become pregnant again. You should avoid pregnancy for at least 3 months after a medical abortion. ▪ DO NOT partake in any strenuous exercise such as horse riding, weight training etc. Ensure patient understands each what is involved with each step and knows what information should be recorded on the sheet – dosage, date and time medicines taken. Reporting adverse drug reactions to the TGA: ▪ In the event a patient experiences an adverse drug reaction to Mifegyne®, the blue **ADRAC card** must be filled out and sent to the TGA. Alternatively, reporting of an adverse event can be done electronically through the TGA's eBusiness Services (https://www.ebs.tga.gov.au/ebs/ADRS/ADRSRepo.nsf?OpenDatabase). ▪ The event should also be reported on the **Medical Abortion Form** and an **Incident Form** and submitted to the Clinical Governance Committee for immediate review.

[redacted]

Medical Abortion Protocol

Nursing Care Session – Administration of Cytotec®

OPTION 1
Misoprostol Administration at Home

Provide patient four (4) tablets of 200mg Cytotec® and pain medication (usually Iboprofen). Ensure patient understands when to take the pain relief medication (Step 2) and the Cytotec® (Step 3) including recording the dosage, date, time and route these were taken.

↓

Prepare patient to be discharged and ensure she has all written instructions and knows the date and time of her follow-up telephone call and appointment. Record these dates and times on the **Patient Instructions for a Medical Abortion** and the **Medical Abortion Form.**

OPTION 2
Misoprostol Administration at Clinic

Prepare patient to be discharged after one (1) hour after the Mifegyne® administration. Ensure she has all written instructions and knows the dates for when:

1. She has to return for the Cytotec® to be administered by the doctor that should be 36-48 hours later
2. The date and time of follow-up telephone call and appointment. Record these dates and times on the **Patient Instructions for a Medical Abortion** and the **Medical Abortion Form.**

↓

Patient must return 36-48 hours for the four (4) tablets of 200mg Cytotec®. Review and assess if patient experienced any side effects and complications after taking the 200mg Mifegyne® and document on the **Medical Abortion Form.**

↓

Administer two (2) tablets of 200mg Ibuprofen and wait for one (1) hour before administering the four (4) tablets of 200mg Cytotec® orally or vaginally. Document the dosage, date and time on the **Medical Abortion Form** and the **Patient Instructions for a Medical Abortion.**

↓

Prepare patient to be discharged and ensure she has all written instructions and knows the date of her follow-up telephone call and appointment. Record these dates and times on the **Patient Instructions for a Medical Abortion** and the **Medical Abortion Form.**

Important discharge information that should be given to the patient:

1. Patient must contact the clinic if they experience any of the following symptoms or signs after taking Cytotec®. There is a link between these symptoms or signs and the presence of an infection.
   a) Severe pain and continuous abdominal pain or cramps
   b) Raised temperature, feel unwell or feverish
   c) Dizziness and confusion
   d) Vaginal discharge smells, is offensive or a different colour.
2. If a miscarriage does not commence within six (6) hours of taking the four (4) tablets of 200mg Cytotec®, it may be necessary to use additional Cytotec®. If this occurs, further doses of Cytotec® will need offered orally or vaginally as two (2) tablets of 200mg Cytotec® [see next page – Outcome 1)
3. What other non-medication strategies they can use to manage their pain at home.
4. They must use sanitary pads (no tampons) to see how much bleeding they have
5. They must not have sex for two weeks after the procedure
6. They must not have a bath, swim or use tampons for 2 weeks after the procedure

[redacted]

Medical Abortion Protocol

[redacted]

Medical Session – Assess the Effectiveness of Medical Abortion	**OUTCOME 1** **Miscarriage doesn't commence within 6 hours of taking Cytotec®** Provide patient additional doses of Cytotec® and pain medication (usually Iboprofen). The further doses of Cytotec® will need offered orally or vaginally as two (2) tablets of 200mg Cytotec® ↓ Prepare patient to be discharged and ensure she has all written instructions and knows the date and time of her follow-up telephone call and appointment. Record these dates and times on the **Patient Instructions for a Medical Abortion** and the **Medical Abortion Form.** **OUTCOME 2** **Miscarriage commences after taking Cytotec®** Review patient to assess if she experienced any side effects and complications after taking the medications document on the **Medical Abortion Form**. See side notes. ↓ Perform an ultrasound to assess if medical abortion successful. Document findings on the patient's **Medical Abortion Form.** ↓ Order pathology testing – serum βHCG – to compare with baseline value. Attach Laboratory Report to patient's **Medical Record** and document findings on the **Medical Abortion Form.** ↓ Prepare to discharge patient if medical abortion successful or refer for a medical abortion if there is a viable pregnancy or there is remaining tissue. Ensure all sections of the **Medical Abortion Form** have been completed. ↓ At the completion of a patient episode, the patient's **Medical Record** should be given to the Quality Manager for review.	Reporting adverse drug reactions to the TGA: ▪ In the event a patient experiences an adverse drug reaction to Mifegyne®, the blue **ADRAC card** must be filled out and sent to the TGA. Alternatively, reporting of an adverse event can be done electronically through the TGA's eBusiness Services (https://www.ebs.tga.gov.au/ebs/ADRS/ADRSRepo.nsf?OpenDatabase). The event should also be reported on the **Medical Abortion Form** and an **Incident Form** and submitted to the Clinical Governance Committee for immediate review. If the ultrasound shows a viable intrauterine pregnancy then refer for surgical abortion. The medications may have caused foetal abnormalities. Serum βHCG levels at two weeks after an abortion of less than 80 IU/L (or less than 20% of base-line level) indicate a successful abortion (Ref 7). If serum βHCG levels are greater than 20% or higher, then refer for surgical abortion – there is a viable pregnancy or remaining tissue. The medications may have cause foetal abnormalities. The Quality Manager will audit all patient cases where treatment with mifepristone and misoprostol is used including recording dosage regimes, outcomes, adverse events and follow up. Reports will be prepared six-monthly to the [redacted] Clinical Governance Committee, Ethics Committee and the TGA.

[redacted]

[redacted]

Medical Abortion Protocol

References

1. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion. Evidence-based guideline No. 7. 2003.
2. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Termination of pregnancy: A resource for health professionals. November 2005.

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5. McIlwraith J and Madden B. Health Care and the Law. Fourth Edition. Thomson Lawbook. Co.2006
6. Australian and New Zealand Society Blood Transfusion. Guidelines for Blood Grouping and Antibody Screening in the Antenatal and Perinatal Setting. Third Edition. March 2007
7. Fiala C *et al.* Verifying the effectiveness of medical abortion; ultrasound versus hCG testing. *European Journal of Obstetrics and Gynaecology Reproductive Biology* 2003; 109(2): 190-195
8. Australasian Society of HIV Medicine. HIV, Viral Hepatitis and STIs – A Guide for Primary Care. 2008 Edition

Attachment 2.

Administration regime for [redacted] at [redacted]

It is proposed to continue established pre procedure protocols for the management of women seeking first trimester pregnancy termination. Patients attending will have initial assessment, including a pelvic ultrasound, comprehensive information regarding the procedure is given and counseling offered. If the patient decides to proceed with a medical abortion, blood group is determined, HCG level, Hb and urine or vaginal swab is collected for chlamydia testing if appropriate. Information is given on pap smears and contraception is discussed and prescribed when required.

Where medical abortion is chosen, those women with pregnancies in the first trimester (up to 63 days LMP) would be treated with mifepristone 200mg orally in the clinic (day 1) and then be discharged home with Misoprostol 800mcg which the patient will take 24- 48 hours later (day 2-3). They are given a further 800 micrograms of misoprostol to be taken (day 4) if the products of conception do not pass (a highly effective regimen researched by Ashok, Kidd et al 2002 and supported by Kulier 2004). All patients will be telephoned by appropriate staff member on day 4 to ascertain if there has been bleeding, and check there are no complications. If there has been no bleeding they will be advised to take the second dose of misoprostol 800 mcg. Patients would receive instructions concerning when and how to access after hours assistance from [redacted] and recommended pain relief. Patients would be required to return to the clinic in 14 days time for ultrasound and requested to have a HCG blood test a few days before the follow up appointment.

Those with a continuing pregnancy at follow up (expected rate 3-4:1000) will be offered a surgical procedure. Those who have retained products of

conception visible on ultrasound at follow up (expected rate 1 or 2:100) will be offered misoprostol 200 or 400 micrograms tds for 2 days as a first line treatment followed by surgical evacuation if the retained products of conception do not pass.

Ultrasound

Ultrasound is performed on all patients before they have a TOP, surgical or medical. In medical patients their gestation cannot be over 63 days LMP.

Pathology

Haemoglobin level is checked on the first visit. A patient with low haemoglobin will be reviewed early if she has heavy and sustained bleeding.

An initial HCG level is obtained on the first visit. If the patient does not return for her check in two weeks then the second HCG level taken at a pathology collecting centre can be used to confirm a successful medical abortion. In a successful termination, we expect that the level will have halved. All efforts will be made to ensure the patient returns for her checkup; however, recalcitrant patients can be monitored by a second blood test to ensure a successful procedure.

Monitoring

[redacted] has a special form "Medical Abortion Form" that will need to be completed and signed off after completion. The Practice manager will be in control of these forms from [redacted]

All complications will be monitored and recorded on the patient's medical record and through the clinic's adverse event form. Serious adverse events will be immediately reported to the HREC and the TGA as a "Serious Adverse Event". Immediate complications will be recorded and documented by the medical practitioner at the clinic. Delayed complications may be encountered either during the follow-up consultation, as a result of telephone contact with the patient, or via feedback from the patient's GP.

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After hours telephone advice

All patients are provided with a discharge letter and instructed to contact the clinic if they have health concerns. After hours, patients can access emergency contact by ringing the clinic numbers which are diverted to our after hours personnel or by ringing [redacted] on [redacted] mobile phone directly.

Tertiary teaching hospitals have an Emergency Department, a 24 hour/day on site obstetric registrar and after hours on call consultant. Women having abortion procedures are provided with a discharge letter and instructed to contact the clinic or to attend an appropriate Emergency Department if they experience problems after discharge.

Follow up

Patients are told to make an appointment for routine follow up care with the clinic two weeks after the procedure. For medical abortion patients it is mandatory that they be followed up at 2 weeks post procedure to be sure that the pregnancy tissue has passed and that there is no retained tissue. They will need to return to the clinic for a repeat ultrasound. Patients will be advised that follow up is VERY IMPORTANT, that their agreement to attend for a follow up appointment is a precondition for mifepristone treatment and that failure to engage in follow up will result in their doctor making efforts to contact them by telephone. The follow up appointment will be arranged at the time of the initial consultation

QUALITY PROCEDURE	[redacted] BOOKING PROTOCOL	Number: QP: 267

- Patient calls and request medical [redacted] receptionist checks gestational age <9 weeks
- Process discussed and patient aware of need for follow up appointment.
- Patient advised to read website for basic information on [redacted]
- Usual booking information e.g. needs photo i.d, bring referral, Medicare card.
- Obtain patient phone numbers and email
- Discuss confidentiality issues and how to communicate with patient
- Screen patient if any medical issues advise to see GP if so
- If lactating to express 2 bottles for day of treatment.

PRELIMINARY TESTS

(To be organised by us, or local GP if possible, 2 days before appointment)

1. Blood group if unknown
2. Pregnancy test
3. Urine Chlamydia
4. FBE / EUC

HPWH to organise

Please email request to patient.

1. Patient can also collect from nurse at clinic.
2. All results to be faxed URGENTLY to clinic

Local Doctors to see patient and organise tests

ALL RESULTS TO BE FAXED TO US ON [redacted]

Change: Version 1		
	Date of Issue:- Dec 2011 Next Review: - Dec 2012	Pages:- 1

QUALITY PROCEDURE	[redacted] PROTOCOL FOR PATIENT ADMISSION	Number: QP: 266

RECEPTIONIST DUTIES:

1. Enter patient details into computer. Please obtain Email address and note any confidentiality issues on file.
2. Photocopy patient I.D and obtain Medicare card.
3. Does the patient have a referral? Obtain the results of tests performed to date. Please place in patient file.
4. Provide paperwork to be filled out by patient.
5. Provide paperwork to be read by patient.
6. Give patient specimen jar and ask to provide specimen of urine.
7. Discuss follow up appointment.
8. Discuss financial consent / method of payment.

PATIENT WILL THEN:

1. Provide a urine sample to confirm pregnancy status.
2. Fill out front page Admission form and Medical History.
3. Fill out [redacted] admission form.
4. Patient needs to read [redacted] patient information'.
5. Patient needs to read 'Who can or cannot have a medical [redacted]
6. Patient needs to read 'Comparison of surgical [redacted] versus [redacted] information sheet'.

NURSE WILL COLLECT FILE AND SEE PATIENT

P.T.O

QUALITY PROCEDURE	[redacted] PROTOCOL FOR PATIENT ADMISSION	Number: QP:

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NURSE WILL TAKE HISTORY

1. Admission paperwork
2. Is this woman certain of her decision?
3. Is this woman suitable for a [redacted]?
4. Abdominal ultrasound to exclude gestations > 9 weeks.
5. Please inform Doctor if > 8 weeks.

NURSE TO CHECK PATHOLOGY

1. Urine BHCG
2. Results to date.
3. Order pathology Including HVS

NURSE TO DISCUSS

1. Process of [redacted]
2. Follow up call
3. Follow up Appointment
4. Complications and when to be concerned.
5. Answer questions

QUALITY PROCEDURE	[redacted] DOCTOR PROTOCOL & FLOW CHART	Number: QP: 264

Doctor consultation and History

- Assess History
- Checks informed consent/answer questions
- Signs Consents
- Discusses patient plan is ok with patient

Doctor examination and tests

- Chest Ausculation? Murmers.
- Abdominal exam? Masses / tenderness
- PV Examination? Uterine size/pelvic tenderness
- HVS and ultrasound to confirm intrauterine gestation <9 weeks
- Bloods taken for quant bhcg, blood group, FBE EUC if not done
- Epiclone to assess rhesus status if required

PTO

QUALITY PROCEDURE	[redacted] DOCTOR PROTOCOL & FLOW CHART	Number: QP: 263

PRESCRIBE ANTIBIOTICS

ANTI-D
Give Anti D if required 250IU IMI.
625 IU for twin gestation.
Patient must sign consent for Anti D first.

CHLAMYDIA
Chlamydia Pos
Azithromycin 1gm orally stat (Ok if breast feeding)
Patient to take in presence of Doctor, Day 1
Treat partner
Follow up in 5 weeks

CHLAMYDIA
Chlamydia status unknown provide script for Azithromycin 1gm PO stat.
Clinic to call patient on day 4 to advise if this needs to be taken. (Earlier if results are available

PATIENT PLAN
Day 1
Mifepristone 200 mg taken orally in precence of Doctor(+/- Azithromycin)
Commence Keflex 500 mg PO tds in afternoon.
Day 2
Fasign 2gm s orally, continue Keflex for rest of week.
Day 3
0800 breakfast and then analgesia pre Misoprostol
Naprosyn 740 mg slow release
0900 Misoprostol 4 tablets sublingually.
Day 4
Follow up call
At 2 weeks
2 week blood test
2 weeks follow up

ROUTINE ANTBIOTICS

Keflex 500mg orally 1 tablet tds 7 days commence Day 1.
Fasign 2 gms orally given day 2. (To avoid nausea)

Patient follow up Day 4.

Discuss results tests (Needs azithromycin?)
Check on bleeding, abdominal pain, fevers.
Has the patient passed the pregnancy?

Attachment 2:

Protocols for use of Mifepristone in both Second Trimester and Cervical priming.

Medical abortion at 10 to 13 weeks gestation

Where medical abortion can be offered, those women with pregnancies of 10 to 13 weeks completed gestation would have 200 mg mifepristone administered in the clinic and arrangements made for admission 1-3 days later to a clinical area where anti emetics and analgesics may be administered according to a nurse initiated protocol as required during the abortion. Blood will be taken for group and hold and misoprostol micrograms per vagina or sublingually administered followed by up to 2 further doses of misoprostol 400 micrograms at three hour intervals (as required) until bleeding and contractions are initiated. Women will remain fasting in the clinical area until products of conception have passed and ultrasound has demonstrated that there is no significant amount of tissue remaining in the uterus. Those who have not passed the pregnancy sac within 6 -8 hours (expected rate 1: 20 as observed amongst 4036 women given this drug combination Ashok, Kidd et al 2002:10) will be managed according to their clinical situation and personal preferences. Those with heavy bleeding or significant pain will be offered immediate surgical evacuation. Those with lesser degrees of bleeding or pain may be offered overnight admission followed by a second attempt at medical abortion next day. Those with no bleeding may be discharged to home with arrangements for readmission for medical or surgical abortion at a later date. Where the sac has passed but ultrasound demonstrates retained products of conception in the uterine cavity, women who are not bleeding heavily may be discharged to home with 6 x 200 microgram misoprostol tablets to be taken with meals tds and instructed to return to a follow up clinic for ultrasound confirmation of completed abortion in 7 days time.

Administration regime; Proposed protocol for second trimester medical abortion

Following appropriate counselling, and where medical abortion can be offered, those women with pregnancies over 13 weeks gestation will have mifepristone 200mg oral administered as outpatients. Women will be admitted 6 – 48 hours later for induction of labour using 800 micrograms of misoprostol per vagina and further doses of 400 micrograms every 3 hours to a maximum of four doses. Immediate access to surgical facilities will be required. Active management of the third stage with cord traction, oxytotics and fundal massage may reduce the number of women expected to require surgical removal of the placenta following delivery of the foetus.

Indication; Cervical priming prior to surgical abortion in the first and second trimesters

Clinical justification

As demonstrated previously, pregnancy is both a life threatening and a serious condition. All pregnancies are both serious and potentially life threatening, and therefore treatments which reduce the risk to the pregnant woman by terminating a pregnancy meet the requirements of Regulation 12B(2) of the Therapeutic Goods Act.

Safety and efficacy of cervical priming with mifepristone

The rate at which serious adverse events occur in surgical second trimester abortions is well documented. Most serious outcomes are consequent to trauma caused by instrumentation. Uterine perforation is diagnosed following fewer than1:1000 abortions (see discussion of safety of first trimester surgical abortion above) and associated uterine artery laceration has occurred in 6/40,000 cases at the [redacted] in [redacted] (unpublished data). These injuries result in serious haemorrhage and may require emergency hysterectomy when they occur in the second trimester. In a South Australian series of 13907 surgical abortions the perforation rate was 0.9%. This rate fell to 0.5% following modification of cervical priming regimens with reduction in mechanical dilation of the cervix at surgery (Mulligan 2006).

Research concerning the effectiveness of cervical priming with mifepristone prior to surgery has studied proxy measures of surgical trauma; the baseline cervical dilation achieved by priming (obviating the need for surgical instrumentation to achieve this dilation) and the force required of the surgeon to pass further dilators through the cervical canal (equating greater force to greater risk of traumatic injury). Ashok, Wagaarachchi et al (2002:9) have reviewed 4 clinical trials involving 340 women who received mifepristone, misoprostol or gemeprost prior to surgery. The baseline cervical dilation achieved was greater with mifepristone than gemeprost, particularly following a delay of 48 hours from treatment, and the force required for further dilation was less following priming with mifepristone priming in comparison to either misoprostol or gemeprost.

Carbonell et al (2007) have reported on a randomised trial which compared misoprostol only (sublingual, vaginal or oral routes) with mifepristone plus misoprostol (sublingual or vaginal) prior to 900 surgical abortion procedures conducted at 12 to 20 weeks. The average cervical dilation achieved with mifepristone priming was 12.5mm +/-2.8mm (95%CI 12.3 – 12.8) while this was significantly less in the misoprostol only groups averaging 8.5mm +/- 3.2mm (95%CI

8.2 – 8.8). Both the requirement for mechanical dilation. The average length of the procedure (a proxy measure of surgical difficulty) was less in the mifepristone treatment groups although this difference did not reach statistical significance.

Administration route dosage duration

Following appropriate counselling, medical and anaesthetic assessment where surgical abortion is offered mifepristone 200mg oral will be administered hours or days prior to admission for surgery. Pre operative cervical ripening will also be undertaken using misoprostol according to the established protocol.

[redacted]
Experimental Drugs Section
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
PO BOX 100
WODEN ACT 2606

2nd July 2009

Dear [redacted],

Re; Mifepristone – 5 Authorised Prescribers at one site seek to vary the protocol to be used in early first trimester abortion

In reply to your letter of 5 March 2009 addressed to [redacted]. Our group of [redacted] medical practitioners have been granted authorised prescriber status to prescribe mifepristone for three indications; first trimester medical abortion, second trimester medical abortion and cervical priming prior to surgical abortion. We submitted four treatment protocols for approval; early first trimester medical abortion up to 63 days gestation, later first trimester medical abortion up to 13 weeks gestation, second trimester medical abortion over 13 weeks gestation and cervical priming prior to surgical abortion at all gestations.

The letters authorising us to prescribe mifepristone stipulated that we must use this drug exactly according to the protocols submitted.

We now seek to vary only one of the four approved protocols.

With growing experience in the use of mifepristone for early first trimester medical abortion up to 63 days gestation it has become clear to us that it is not always appropriate to administer mifepristone and misoprostol at the same time. Instead we would prefer to adopt a more widely used protocol in which there is a delay between mifepristone administration and misoprostol administration of 24-48 hours.

The protocol which is currently approved for our use is as follows;

Medical abortion up to 63 days from last menstruation

Where medical abortion can be offered, those women with pregnancies of 9 completed weeks gestation or less who choose this option would have mifepristone 200mg oral and misoprostol 800 micrograms per vagina administered in the clinic and be discharged to home with a further 800micrograms of misoprostol to be taken orally or vaginally next day if the products of conception do not pass. In addition women would receive written and verbal instructions concerning when and how to access further medical assistance after hours, what pain relief to take and routine follow up instructions to return to the clinic in 7 days time for ultrasound or quantitative beta HCG testing to confirm completed abortion. Those with a continuing pregnancy at follow up (expected rate 3-4:1000) will be offered a choice of repeat medical treatment or a surgical procedure. Those who have retained products of conception visible on ultrasound at follow up (expected rate 1 or 2:100) will be offered misoprostol 200 or 400 micrograms tds for 2 days as a first line treatment followed by surgical evacuation if the retained products of conception do not pass.

[redacted]

The protocol which we seek approval to use is as follows;

Medical abortion up to 63 days from last menstruation

Where medical abortion can be offered, those women with pregnancies of 63 days gestation or less who choose this option would have mifepristone 200mg oral administered in the clinic and be discharged to home to self administer misoprostol 800 micrograms per vagina after 24 to 48 hours with a further 800micrograms of misoprostol to be taken orally or vaginally on the next day if the products of conception do not pass.

In addition women will receive written and verbal instructions concerning when and how to access further medical assistance after hours, what pain relief to take and routine follow up instructions for ultrasound or quantitative beta HCG testing to confirm completed abortion. Those with a continuing pregnancy at follow up (expected rate 3-4:1000) will be offered a choice of repeat medical treatment or a surgical procedure. Those who have retained products of conception visible on ultrasound at follow up (expected rate 1 or 2:100) will be offered misoprostol 200 or 400 micrograms tds for 2 days as a first line treatment followed by surgical evacuation if the retained products of conception do not pass.

Evidence supporting the efficacy and safety of the proposed protocol and comparison between the approved protocol and the proposed one.

The proposed protocol is in extensive use in the United Kingdom and the United States of America. It is endorsed by the Royal College of Obstetricians and Gynaecologists in the evidence based guideline on "The Care of Women Requesting Induced Abortion" and is set out in Recommendation 43 (p52) and supported by evidence presented in Evidence Table 12 (p 76 – 77). The entire guideline was provided with our original application, we have attached only the relevant pages on this occasion.

In the United States of America a similar protocol is used extensively. We have attached a review of 95,163 early medical abortions which were conducted by administration of 200mg of mifepristone in the clinic followed by self administration of 800 mcg misoprostol after 24 to 72 hours at gestations up to 49 days and after 24 to 48 hours at gestations 50 to 63 days (Henderson et al 2005:176).

The approved protocol (200mg mifepristone with 800mcg misoprostol administered on the same day) has been compared with the one we seek to adopt (200mg mifepristone with 800 mcg misoprostol administered after 24 to 48 hours) in two randomised controlled trials. Guest et al 2006) gave the misoprostol at either 6 hours or 36 to 48 hours later to two groups of 225 women and found the delayed misoprostol dose provided higher efficacy. Creinin et al (2004) compared the same two treatment regimens amongst 1080 randomly assigned women to find that there was no statistical difference in effectiveness. A smaller series of 120 women given mifepristone 200mg with misoprostol administered buccally at the same time had a lower than expected

[redacted]

completed abortion rate and the authors (Lohr et al 2007) concluded that this regimen did not warrant further study.

Our reading of the evidence presented is that both protocols (the approved one and the proposed one) are effective. There may be a higher rate of completed abortion when misoprostol treatment is delayed (proposed protocol), however the main advantage would be the convenience for patients who would have the opportunity to choose which day to set aside for bleeding and cramping. This then provides the best circumstances for the woman to be in a comfortable environment with the support of an appropriate person.

Please find attached;

1) Agreement to Treatment Directions Agreement forms signed by each of 5 medical practitioners in which we have nominated only the indication for which we seek variation to the protocol.
2) A support letter from the Ethics of Human Research Committee of the [redacted]
3) Hard copies of the original research papers referred to.

If any further information or clarification is required, please do not hesitate to contact me either by mobile telephone [redacted] or by e-mail [redacted].

Yours sincerely,

[redacted]

[redacted]

Attachment 2:

Protocol for the use of Mifepristone in 2nd trimester of pregnancy.

As per the decision of the [redacted] Human Research Ethics Committee on 5th Dec 2011

Indication.
Management of fetal death in utero and termination of pregnancies with severe abnormalities in the second trimester of pregnancy at [redacted]

Dosage. Two tablets of 200mg Mifepristone.

Administration.

Orally, 36 hours before admission to [redacted] for Cervagem (Gemeprost) protocol.

Day of Treatment:
All patients will have a high vaginal microbiology culture done and will receive prophylactic antibiotics. Cervagem pessaries will be placed vaginally every 3 hours up to a maximum of 5 per day.

Follow Up:

Patients will require close physical and emotional follow-up. All patients will be followed up by a qualified counsellor and medical follow up will be based on the physical condition of the patient. If there are risk factors for infection or retained products of infection then the patient will be seen within five days.

[redacted]

Mifepristone and misoprostol for medical termination of pregnancy

Indications and regimens for prescription and use of the unapproved product Mifepristone, 200mg tablets at the [redacted]

9 June 2011

Indications for use of mifepristone

Mifepristone is to be used for termination of pregnancy where medical abortion is assessed clinically as the most appropriate method for the woman, including where surgical abortion is not clinically indicated or available. This is of particular importance where there is evidence of a fetal abnormality or intrauterine fetal death.

Site of prescription and use

Care will be provided at the [redacted] Specifically the mifepristone and misoprostol will be administered under direct medical supervision. It is anticipated that the vast majority of women treated will proceed to complete the abortion on the premises. In exceptional cases, if abortion does not occur or is not complete within a few hours of misoprostol, outpatient follow up will be arranged, or if appropriate, surgical evacuation of the uterus will be arranged.

Regimens to be used

The following regimens will be used, as recommended by the Royal College of Obstetricians and Gynaecologists (RCOG), the International Federation of Obstetrics and Gynaecology (FIGO) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).

Up to 63 days gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- A further dose of 400 µg misoprostol administered orally or vaginally if products of conception not passed within 4-6 hours.

63-91 days gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- Further doses of 400 µg misoprostol administered orally or vaginally at 3 hourly intervals up to a maximum of five doses if products of conception not passed.

13-24 weeks gestation:

- 200mg mifepristone orally, swallowed under supervision
- 36-48 hours later 800µg misoprostol administered vaginally
- Further doses of 400 µg misoprostol administered orally at 3 hourly intervals up to a maximum of four doses if products of conception not passed.
- Consideration of a repeat course of treatment if unsuccessful.

After 24 weeks gestation:

- As for 13-24 weeks gestation, but dosage of misoprostol may be reduced and intervals increased as judged appropriate by the clinician.

Potential variations may be made according to clinical judgment in individual cases, or if new evidence supports a change e.g. administration of misoprostol sublingually:

- Substitution of gemeprost for misoprostol in accordance with RCOG guidelines and approved UK regimens. This may be necessary especially when two cycles of misoprostol administration have not been effective. Gemeprost may have to be added to the regimen in the 3rd cycle.

The [redacted] has procedures in place to ensure that informed consent is obtained and to support delivery of care, provision of information and appropriate follow up.

Failed medical abortion

As with failed surgical abortion, if medical abortion fails, there needs to be clinical discussion about how best to proceed to complete the termination. Options might include a further course of mifepristone and misoprostol or gemeprost, surgical abortion, intrauterine injection with a range of agents or even hysterotomy, depending on the particular clinical circumstances.

Monitoring and reporting

A record will be kept and audit will be undertaken of all cases where treatment with mifepristone is used, including recording of dosage regimens, outcomes, adverse events and follow up. Reports will be made six monthly to the Clinical Ethics Committee. Suspected adverse events will be reported to the TGA, the sponsor and the HREC.

Revisions to practice, information and consent forms

New evidence may lead to changes in treatment regimens. Any necessary changes will be reviewed and approved prospectively by [redacted] and notified to the HREC.

Clinical justification

Background

The [redacted] provides abortion services under the consistent with the legal jurisdiction of the State of [redacted]. Two medical practitioners are required to support the case to offer termination of pregnancy and this is to be endorsed by the Chief Medical Officer of the Service.

Currently, all termination of pregnancies under 14 weeks gestation are carried out surgically by a limited number of Specialists in Obstetrics and Gynaecology in the department. For pregnancies warranting termination after 14 weeks gestation, the process is induced by the administration of misoprostol vaginally. The success of the termination process has been variable and it is felt that the addition of Mifepristone to the regimen, as evidenced in the literature, will shorten the induction to delivery interval, preventing prolonged hospital stay and the psychological distress associate with it.

Efficacy and safety data

Mifepristone

Mifepristone is a synthetic anti-progesterone, which has been shown to be an effective abortifacient when combined with a prostaglandin administered one to three days later.

Misoprostol

Misoprostol is a prostaglandin which has been widely used in combination with mifepristone to induce termination of pregnancy.

Regulatory approvals

Mifepristone (the subject of this application) has been registered and widely used for medical abortion in many countries around the world, including many with a regulatory standard comparable to that in Australia, for example USA (registered in 2000), UK (1991), Sweden (1992) and New Zealand (2001). Where mifepristone is registered for pregnancy termination, its use is approved in conjunction with a prostaglandin.

The company which manufactures misoprostol (the prostaglandin proposed to be used in conjunction with mifepristone) has not sought a licence anywhere for its use in pregnancy termination, but it is available "off-label" and is widely used in gynaecological practice throughout the world, including in Australia.

Together with mifepristone, misoprostol constitutes part of the licensed regimen for early medical abortion in the USA. Mifepristone with misoprostol is

recommended as the optimal regimen for medical abortion by the UK Royal College of Obstetricians and Gynaecologists (RCOG)(1), although the licensed combination in that country is mifepristone in combination with vaginal gemeprost. The approved regimen for early pregnancy termination with mifepristone in New Zealand includes oral misoprostol or vaginal gemeprost.

Mifepristone and misoprostol in Australia

Mifepristone is not available in Australia. We propose to use Mifegyne, sourced from Istar.

In Australia misoprostol is used when indicated for cervical priming prior to surgical abortion or curettage for miscarriage and for medical abortion in the second trimester of pregnancy, in accordance with the published medical literature. These uses are "off-label", but because misoprostol has been approved for other (gastrointestinal) indications, it is available to prescribers without special application. It is proposed to use Cytotec, sourced from Pfizer.

Reasons for choice of misoprostol as prostaglandin

The main alternative to misoprostol is gemeprost, which is approved in Australia for second (but not first) trimester termination of pregnancy.

A series of comparative studies in the mid to late 1990s found no advantages of gemeprost compared to misoprostol and some suggested a worse side-effect profile. Since then, in the published literature misoprostol has largely replace gemeprost for medical abortion in the first, second and where information is available third trimesters. Misoprostol is included in the licensed regimens for medical abortion in some countries and is the recommended "optimal" prostaglandin in the RCOG guideline.

Misoprostol is preferred to gemeprost because:

- It is stable at room temperature and therefore easier to safely store and transport than gemeprost, which must be stored frozen.
- Misoprostol can be given orally, sublingually or vaginally: some women find oral or sublingual administration more acceptable(2).

Evidence for safety and efficacy of mifepristone with misoprostol

As stated above, mifepristone has been approved/registered/licensed for use in pregnancy terminations in many countries, in some cases with misoprostol and in others with gemeprost.

It is estimated that at least 500,000 medical abortions have been conducted in the USA and over 1.5 million in Europe.

A number of papers report on the Australian context and about experience following the introduction of medical abortion in several European countries(3, 4). One study has reported on the use of mifepristone in Australia(5).

There is an extensive body of research and clinical evidence supporting the use of mifepristone together with misoprostol for termination of pregnancy.

Much of this literature has been reviewed in the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)'s "Termination of pregnancy: a resource for health professionals"(6) and the Royal College of Obstetricians and Gynaecologists (RCOG) guideline(1). These documents remain current.

Medical versus surgical abortion

There is an extensive body of literature reporting outcomes of medical and surgical abortion, but there are few randomized controlled trials comparing medical and surgical methods of abortion, because women usually have a clear preference for one or other method. The following summary is drawn from the RCOG guideline(1) and the RANZCOG information resource(6), which contain more detailed references.

Surgical abortion in the first trimester

- 100% have a surgical procedure
- Failure rate ~2.3 per 1,000, higher before 7 weeks
- Repeat curettage ~1-2%
- Symptomatic infection up to 10%, usually not serious
- Uterine perforation 1-4 per 1,000
- Cervical trauma <1%
- Haemorrhage requiring blood transfusion estimated 1-2 per 1,000
- Mortality estimated around 1 per 100,000

Medical abortion (most data up to 63 days gestation)(7)

- Experience of pain and bleeding similar to miscarriage
- Pain and bleeding probably more prolonged than for surgical abortion
- Drug side effects may include nausea, vomiting, diarrhoea and fever
- Up to 5% have a surgical procedure, mainly for incomplete abortion
- Failure rate (continuing pregnancy) ~1%, generally thought to increase with increasing gestation
- Infection rates probably lower than for surgical abortion
- Minimal perforation or cervical trauma unless surgery required
- Haemorrhage requiring transfusion comparable to surgical abortion
- Mortality estimated around 1 per 100,000

Medical abortion in the late first trimester (9-13 weeks)

- Reports suggest that similar outcomes can be achieved to those described above for earlier medical abortion, although repeated doses of prostaglandin may be required(1, 6, 8)

Second trimester abortions(1, 6, 9-12)

Most studies conclude that complication rates tend to increase with gestation for both medical and surgical methods of abortion. Comparative data are very limited and practice is strongly influenced by practitioner experience and preference.

Very low complication rates can be achieved for surgical abortion in the late midtrimester in expert hands. Special expertise and particular staff attitudes are required at more advanced gestations and the RCOG notes that "for gynaecologists lacking the necessary expertise and case load, and for their patients, mid-trimester medical abortion using mifepristone plus prostaglandin is appropriate".

Mifepristone in the third trimester(1, 6, 13-17)

The evidence presented indicates that the use of mifepristone is not associated with more maternal complications when used in the third trimester compared with use at earlier gestations. Furthermore the evidence suggests that the use of mifepristone with prostaglandin for induction of labour is more efficacious than currently standard treatment (artificial rupture of the membranes and oxytocin or prostaglandins alone), in terms of the interval from induction of labour to delivery. This reduced induction-delivery interval may reduce the medical risks to the mother, for example, reduced risk of infection, reduced risk of disseminated intravascular coagulation. The evidence available would suggest that a regimen for induction of labour using mifepristone with misoprostol is likely to be more efficacious than those currently available to us so that if it were not for the potential (unknown) fetal effects it may be considered as the preferred regimen in all women requiring induction of labour.

Mifepristone and miscarriage

Various regimens are used in the medical management of miscarriage, most involving misoprostol and some advocating routine inclusion of mifepristone. The place of mifepristone is not yet clear, but it may well have a place in some cases(18, 19).

Mortality

In 2006, five deaths due to a rare fatal infection with clostridium sordellii were reported in the USA following early medical abortion with mifepristone and misoprostol among an estimated total of over 500,000 procedures(20). A similar death has been reported in Canada, but there are no known reports of such cases in Europe among an estimated 1.5 million procedures.

These data suggest a mortality rate following medical abortion of around 1:100,000 in the USA, although rates appear to be lower in Europe. Mortality following surgical abortion is generally quoted at around 1:100,000 in Western countries, but it is probably even lower when considering procedures only in the first 9 weeks of pregnancy. Overall mortality associated with childbirth is around 1:10,000.

One further case of fatal clostridium sordellii toxic shock after medical abortion has been reported in the USA, together with one associated with miscarriage and two fatal cases of clostridium perfringens infection after medical abortion(21, 22). This is consistent with mortality rates around 1:100,000 in the USA.

Choice of method

- RCOG considers that ideally abortion services should be able to offer a choice of recommended methods
- Women who prefer surgical methods like the same-day time course and may prefer general anaesthesia
- Women who prefer medical methods want to avoid a surgical procedure and/or anaesthesia and can tolerate the anticipated miscarriage symptoms, uncertain time frame and repeated visits

Long term outcomes and complications

These are reviewed, together with the limitations of the available information in the RCOG guideline(1) and the RANZCOG information resource(6). Most of the available information relates to surgical abortion and comparative data are very limited, but do not suggest any differences between likely outcomes of surgical and medical abortion.

Different regimens for medical abortion(1)

Many regimens for medical abortion have been studied and compared. These are summarized in the RCOG guideline and its evidence tables. The evidence is clear that mifepristone/prostaglandin regimens are preferable to prostaglandin alone or methotrexate/prostaglandin regimens in their efficacy and time course of action. RCOG concludes that "single agent regimens do not have a place in UK practice where mifepristone is readily available". This includes in the second trimester, when case series of terminations with misoprostol alone report longer induction-delivery intervals than those achieved with mifepristone-misoprostol combinations.

[redacted]

ADMINISTRATION AND MONITORING REGIME.

MIFEPRISTONE & MISOPROSTOL

The patient is offered counselling and full information is given on the regime, possible side effects and consent is obtained.

The patient is given 200mg of mifepristone at consultation.

A prescription for metoclopramide hydrochloride (Maxalon) 10 mg tablets. 1 tablet every eight hours to be taken if nausea and vomiting exceeds 24 hours.

The patient is given four misoprostol 200mcg tablets to be taken buccally (between the gum and the cheek), 24 - 48 hours after the dose of mifepristone. The patient is given a 24 hour emergency telephone number to contact [redacted] or [redacted] in case of emergency.

EFFICACY/SAFETY DATA

Mifepristone is a safe effective medical abortifacient that is registered for use in 33 countries around the world. Since it was first registered for use in France in 1988, approximately 2 million women in Europe and North America have been prescribed the drug to terminate unplanned and unwanted pregnancy.

In 2004, the Royal College of Obstetricians and Gynaecologists UK 'Guidelines for the Care of Women requesting Induced Abortion recommended the use of mifepristone plus prostaglandin as the most effective and safest method for terminating pregnancies of less than 7 weeks gestation.

Some minor allergic reactions have been reported including rash, hives and itching however no casual relationship between these events and mifepristone has been established.

Side effects -as the treatment is to produce an abortion, the vaginal bleeding and uterine cramping necessary to produce an abortion are expected consequences.

Other common side effects are nausea, vomiting and diarrhoea which are resolved very quickly. If nausea and or vomiting exceed 24 hours, the patient will be instructed to take Maxalon 10 mg tablet 1 every 8 hours for two days. If the nausea and vomiting still continues or the patient is concerned, then she will contac[redacted]

[redacted]

Diarrhoea will resolve spontaneously.

PROTOCOL:

All patients are referred to [redacted] by a medical practitioner. The patient makes her own appointment for consultation and treatment. Most patients will be seen in one to two days after the initial phone call.

CONSULTATION: DAY 1

1. The patient is seen up to 49 days from the date of the last menstrual period. She will be given an ultrasound to confirm dates of the pregnancy.
2. Counselling will be offered and encouraged.
3. A full medical and surgical history will be taken (see Appendix IV). During this consultation it will be determined if the patient has any of the following which will contraindicate this treatment or identify contraindications to the drug:

- Hemorrhagic disorder, or anticoagulant therapy;
- Chronic renal failure;
- Concurrent long-term corticosteroid therapy;
- Confirmed or suspected ectopic pregnancy or adnexal mass;

- Inherited porphyrias;
- IUD in place;
- Rh status, quantative βCG haemoglobin as indicated;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Pap smear and vaginal swab for STD as indicated at consultation, or at patient's request.
- Unwillingness to undergo surgical abortion, in the event that the medical abortion fails, and
- Unwillingness to discontinue Breast feeding for 72 hours after taking mifepristone

It will be determined if the patient's gestation is no more than 49 days from her last menstrual period (LMP). This will be confirmed by ultrasound and clinical evaluation.

The procedure will be explained in detail to the patient.

4. Full open disclosure of the side effects and possible complications will be discussed.

This will include:

- Stomach cramps;
- Severe vaginal bleeding;
- Prolonged vaginal bleeding – up to 9 – 16 days;
- Nausea, vomiting and diarrhoea;
- The need for the patient to return for a further consultation in approximately 14 days;
- An explanation of why tampons should not be used during this time and advice on not having vaginal sex until seen by [redacted] at the final consultation;
- Regime and information for taking analgesics, and
- Instructions.

5. The patient will be given written instructions on when to take misoprostol (see Appendix II).
6. Signed consent will be obtained (see Appendix I).

7. Contact details for [redacted] – mobile phone number, answering service and Clinic phone number. Contact details for [redacted] if there is an emergency.
8. Information on contraception following abortion. Patients may take oral contraception even if they are still bleeding. Insertion of Intra-uterine device (IUD) can take place at the follow-up consultation. Patients who choose tubal ligation will be referred as appropriate to avoid delays.
9. [redacted] will ensure that the patient has given her correct contact details.
10. The patient will be advised that she must attend for a follow up appointment 2 days after taking misoprostol or an arrangement can be made for the patient to be contacted by phone.
11. The patient will be informed that she **must** attend here Day 14 follow-up, otherwise she will be contacted by the Clinic.

CONSULTATION – 2 days after taking misoprostol

Follow up visit to exclude infection, incomplete abortion and therapeutic failure. The patient may be contacted by phone which will be arranged at the initial consultation.

CONSULTATION - DAY 14

Follow up visit to assess completion of abortion.

- Take history of patient's description of bleeding;
- Test for declining levels of βCG levels if indicated;
- Patient will be given an ultrasound;
- If pregnancy is ongoing the patient will be required to undergo Dilatation and Curettage as soon as possible, and

The results of pap smear and vaginal swabs for STD, if taken at Day One consultation, are reviewed and managed as appropriate.

Further follow up.

First follow up will be two days post taking misoprostol either by consultation or by phone.

The patient will be contacted by the Clinic if she doesn't keep her **DAY 14** follow-up appointment.

The patient is instructed to return for a further consultation if bleeding persists beyond 4 weeks or becomes heavy again.

Patients are eligible for mifepristone if :

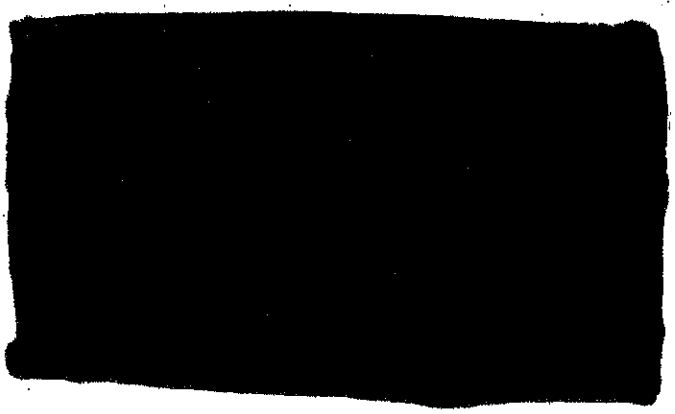
-it is deemed that it is legal for that individual patient to have a termination in [redacted]
-they are no more than 9 weeks 0 days LMP on ultrasound. Also the ultrasound must show a pregnancy in the uterus and not an ectopic pregnancy.
-they have no contraindications (see Contraindications MTOP.ind)
-they live no further than 30 minutes from a hospital, have reliable transport and have access to a reliable telephone
-they consent to have surgery if the medical termination fails or there is significant retained tissue

Mifepristone, 200mg is given orally by the doctor [redacted]
The patient is instructed to take 4X200mcg of misoprostol 24 to 48 hours after the initial mifepristone,The misoprostol can be take buccally (hold for 30 minutes and then swallow remaining tablets with water) or vaginally.Patients are encouraged to take analgesia before the misoprostol and a small amount of panadiene forte (4) tablets and maxalon (3 tablets) are given to the patient to take if necessary.

At the first appointment all patients are checked for chlamydia and gonorrhoeae. Their blood group is ascertained and anti -D is given to RH negative women. Hb and bhcg level are also checked.

Patients are contacted by [redacted] 1 to 2 days after the misoprosol. If they aren't reachable on the phone a text message is left. All patients are given [redacted] mobile phone number to use if there are any problems or concerns. They are also given a summary of problems that indicate when they should contact [redacted] Patients also have a letter for hospital if there are significant problems.

Patients are advised that they need to return to the clinic in 2 weeks for a check to be sure the pregnancy has been terminated and that there isn't significant retained tissue and that there is no infection. If patients do not return , they are texted at 2 and then 3 weeks to remind them to have a check. If they still don't return they are sent a letter with a pregnancy testing kit , by registered mail.



If you have any of the following conditions you CANNOT have a medical termination (MTOP)

Chronic adrenal failure

Haemorrhagic/bleeding disorder

Inherited porphyria

Severe anaemia

Long term anticoagulant therapy (eg warfarin, heparin)

Corticosteroid therapy (eg prednisone, cortisone)

Confirmed or suspected ectopic (tubal) pregnancy

Allergy to mifepristone or misoprostol

IUD in place — this must be removed first

Irritable bowel disease or uncontrolled bowel disease (eg severe diarrhoea, Crohn's disease)

Serious systemic illness (eg severe liver disease, heart disease, kidney failure, uncontrolled seizure disorders)

Serious pelvic infection

Unwillingness to undergo a surgical termination

Other important considerations

You can only have a medical termination if you are no more than 9 weeks pregnant.

You MUST return to the clinic in two weeks.

Live within 30 minutes of a hospital and have reliable transport.

Have a reliable telephone.

Consent to a surgical termination if the medical termination fails (at no extra cost).

[redacted]

[redacted]

[redacted]

When you should call us

You can call us at anytime if you are worried but these are the particular things you should lookout for.

You are soaking two super pads per hour for two consecutive hours.

If you have a temperature over 38 in the days after taking the misoprostol.

Severe abdominal pain, flu-like symptoms, feeling significantly unwell.

[redacted]

Attachment 2:

[redacted]

CLINICAL POLICIES, PROCEDURES & GUIDELINES

Misoprostol and mifepristone for medical termination of pregnancy and or fetal death

1. OPTIMAL OUTCOMES

To provide complete medical termination of a first, second or third trimester of pregnancy or fetal demise in the first, second or third trimester of pregnancy, with a short induction to delivery interval.

2. PATIENTS

- Pregnant woman requiring a medical termination of pregnancy in the first, second or third trimester, or induction of labour after intrauterine fetal demise in the first, second or third trimester
- **The use of mifepristone at [redacted]s restricted to greater than 12 weeks gestation, apart from a few specific situations such as:**
  - o Women requiring early pregnancy interruption in whom surgery is risky (e.g. significant maternal cardiac disease with an unplanned pregnancy or fetal anomaly) or surgical evacuation is potentially difficult (e.g. previous difficult or failed mechanical dilatation or Asherman's syndrome.
  - o Whereby there is a fetal anomaly or fetal demise in the first trimester whereby medical termination is preferred for histopathological examination of the placenta or fetus.

3. STAFF

- Registered midwives
- Student midwives
- Registered nurses
- Medical staff
- Social worker

4. EQUIPMENT

- Nil

5. CLINICAL PRACTICE

- Counsel the woman appropriately.
- Ensure the woman meets the criteria for medical termination of pregnancy.
- Accurate gestational assessment is essential.
- Ensure woman fulfils the criteria for termination of pregnancy under [redacted] guidelines.
- Approval for termination of pregnancy must be sought from Termination Review Committee if required; see "Guideline for Termination of Pregnancy at the [redacted]
- All women should be given accurate written information about treatment. (Information sheet for women: Mifepristone/ Misoprostol induction of labour (Attachment A)
- Obtain consent using consent form attached to this guideline (including for potential evacuation of retained products of conception) and document

Choice of methods includes:

- mifepristone and misoprostol
- misoprostol alone
- gemeprost alone

A. Mifepristone (RU486) and Misoprostol (Cytotec) Regimen

- Administer Mifepristone (RU486) 200 mg orally as an outpatient, as prescribed by a medical officer authorised by the Therapeutic Goods Administration (TGA). Under exceptional circumstances the woman may have to stay in hospital.
- The woman is to take the prescribed Mifepristone orally, preferably 36-48 hours before her planned admission for Misoprostol administration.
- If the dose is vomited another dose can be given (a wait of 30-60 minutes is suggested).
- Organise return admission 24-48 hours after mifepristone (RU486) (given written information as to when and where to return to hospital. (On patient information sheet).

On admission:

- Take a blood sample for group and hold.
- Ensure adequate analgesia. Epidural is not contra-indicated in these circumstances
- Arrange follow up
- Administer misoprostol (Cytotec) vaginally or orally according to table

Dosage and administration of Misoprostol when used after Mifepristone 24-48 hours previously

Misoprostol (Cytotec)	<13 weeks gestation*	13-20 weeks gestation*	21-28 weeks gestation*	29-34 weeks gestation	>34 weeks gestation
Initial dose	800 micrograms PV	800 micrograms PV	400 micrograms PV	100 micrograms PV	100 micrograms PV
Subsequent dose	400 micrograms PER VAGINA every three hours to a maximum of TWO doses	400 micrograms PER ORAL Or PER VAGINA every three hours to a maximum of FOUR doses	400 micrograms PER ORAL or PER VAGINA every three hours to a maximum of FOUR doses	200 micrograms PER VAGINA every FOUR hours to a maximum of FOUR doses	100 micrograms PER VAGINA Every FOUR hours to a maximum of FOUR doses

***NOTE: Women with a previous scar consider halving the dose of misoprostol, especially in presence of a dead fetus <28 weeks gestation**

Contraindications

- Severe asthma requiring corticosteroids
- Chronic or acute adrenal or hepatic failure
- Bleeding disorders of concurrent anticoagulation therapy
- Known allergy to mifepristone
- Suspected ectopic pregnancy
- IUCD in situ (to be removed before treatment)
- Inherited porphyria

Side effects

- Nausea and vomiting 15-20%
- Headache 15-20%
- Occasional pelvic cramping before admission
- Pelvic infection (rare), or systemic infection

B. Where Mifepristone (RU486) is not used

- Obtain consent and inform the woman of likely longer induction to delivery interval and need to remain as an in-patient and document.
- Take a blood sample for group and hold.
- Administer vaginally one of the following options:

Medication	12- 28 weeks	29-34 weeks		>34 weeks
Misoprostol (Cytotec)	400 mcg PV, 3 hourly maximum of 5 doses	100 mcg Initially PV, then 200 mcg 3 hourly PV to a maximum of 5 doses		100 mcg PV 4 hourly to a maximum of 5 doses
Gemeprost	1 mg PV 3 hourly to maximum of 5 doses	Use with caution		Not recommended
Prostin	Not recommended	2 mg initial dose PV	2 mg, 6 hours later PV	According to Bishop's score

If not delivered after any of the regimens above:

- Rest woman overnight and recommence regimen the following day.
- In addition, a repeat dose of mifepristone can be given after two days of misoprostol treatment.
- Alternative regimens include high dose Syntocinon, extra-amniotic PGF2a, or gemeprost.

Third stage of labour for all women:

- Administer 10 units of Syntocinon IM into the maternal thigh after delivery of the fetus.

After Discharge from hospital:

- Contact the woman 48-72 hours after discharge from hospital to enquire specifically about the following symptoms of infection: nausea, fever, chills, vomiting, diarrhoea, offensive vaginal discharge, or increasing bleeding. The phone call is to be made by the midwife who is caring for the woman in a continuity of care model, or otherwise by either the [redacted] or the [redacted]
- Review any woman with symptoms of infection in delivery suite within the next 4 hours. The review must be undertaken by a medical officer, with consideration to the administration of antibiotics when indicated.

6. HAZARDS/SUB-OPTIMAL OUTCOMES

- Unsuccessful or incomplete termination
- Long induction to delivery interval
- Uterine rupture
- Infection
- Inadequately managed pain

7. DOCUMENTATION

- Integrated clinical notes
- ObstetriX

8. EDUCATIONAL NOTES

- Misoprostol (Cytotec) is 300 times cheaper than Gemeprost (30cents versus $92), generally has fewer side effects and can be stored at room temperature for several years.
- Mifepristone (RU486) is the only anti-progestin that is internationally approved for the induction of abortion[4]. Mifepristone (RU486) binds to progesterone receptors to reverse their inhibition of cervical softening and dilation, and uterine contraction. More importantly, it sensitizes the myometrium to prostaglandins[4&5]. The maximum effect of mifepristone (RU486) is achieved when prostaglandins are administered 36-48 hours after mifepristone (RU486) dose[4].Mifepristone (RU486) pre-treatment prior to administration of prostaglandin analogues can be given to prime the uterus. It has been shown to have the following benefits:
    - increase abortion rate within 24 hours.
    - reduce curettage rate for retained products.[2]
    - reduce induction to abortion interval.
- There is a 0.2% rate of abortion after mifepristone (RU486) administration prior to treatment with prostaglandins[3].
- In women given mifepristone (RU486) pre-treatment, 97% will abort within 5 doses of prostaglandins[3]. Abortion rate and induction-to-abortion interval for 200mg and 600mg doses of mifepristone (RU486) have been found to be the same[6]. Common side effects of the prostaglandins misoprostol (Cytotec) and gemeprost, are:
    - 50% of women get a fever
    - 20-25% suffer from nausea, vomiting, dizziness, diarrhoea or headache[1].
- The safety and efficacy of Mifepristone used in conjunction with a prostaglandin analogue usually misoprostol, is well established, as the best available regimen for medical termination of pregnancy. The Therapeutic Goods Authority (TGA) has given authorised prescriber status to listed medical practitioners at [redacted] to prescribe Mifepristone for this purpose. The Human Research Ethics Committee has reviewed the request for Authorised Prescribers and has endorsed certain doctors at the [redacted] for the purpose of being an Authorised Prescriber of Mifepristone under subsection 19(5) of the Therapeutics Goods Act.
- Gemeprost (Cervagem) is the only synthetic PGE1 analogue licensed for mid-trimester termination of pregnancy (TOP) Misoprostol (Cytotec) is a synthetic PGE1 analogue only licensed for the prevention and treatment of peptic ulcer disease. However, it is commonly used for cervical priming, medical abortion and induction of labour7.
- Misoprostol is not licensed for use in pregnancy in Australia, although it has been used extensively both within Australia and worldwide for termination or pregnancy and for induction of labour. The woman should be informed of this.
- There is no evidence that Gemeprost is more fetotoxic than any other prostaglandin analogue.
- Serious infection is an uncommon complication of medical abortion or induction of labour. There have been rare cases of serious infection, including death, after birth in women who have delivered after use of misoprostol and mifepristone (from *Clostridium sordellii and Clostridium perfringens*, and Group A streptococcus). To date, no causal link with mifepristone or misoprostol has been made. All women must be made aware of the risks of infection and be advised to present to hospital immediately if they have symptoms of infection. Potential infection should be investigated and treated appropriately.

9. RELATED POLICIES/ PROCEDURES/CLINICAL PRACTICE GUIDELINES

- Termination of pregnancy

10. REFERENCES

1. Wong, K.S., et al. (1998). Vaginal misoprostol compared with vaginal Gemeprost in termination of second trimester pregnancy: a randomized trial. Contraception, 58(4): 207-210.

2. Bartley, J. and D.T. Baird (2002). A randomised study of misoprostol and Gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. British Journal of Obstetrics and Gynaecology, 109: 1290-1294.
3. Ashok, P.W., et al. (2004). Mid-trimester medical termination of pregnancy: a review of 1002 consecutive cases. Contraception, 69: 51-58.
4. Lalitkumar, S., M. Bygdeman and K. Gemzell-Danielsson (2007). Mid-trimester induced abortion: a review. Human Reproduction Update, 13(1): 37-52.
5. Fiala, C. and K. Gemzell-Danielsson (2006). Review of medical abortion using mifepristone in combination with a prostaglandin analogue. Contraception, 74(1): 66-86.
6. Webster, D., G. Penney and A. Templeton (1996). A comparison of 600 and 200mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. British Journal of Obstetrics and Gynaecology, 103: 706-709.
7. Ngai, S.W., O.S. Tang and P.C. Ho (2003). Prostaglandins for induction of second trimester termination and intrauterine death. Best practice & Research in Clinical Obstetrics and Gynaecology, 17(5): 765-75.

Appendix A

- Patient information leaflet to be attached here

ATTACHMENT 2 [redacted] (4) 195

PROTOCOL FOR MEDICAL ABORTION

On presenting to the clinic for the initial consultation, it is then established why the woman is requesting an abortion. The woman may decide to have an abortion after consideration has been given regarding her personal circumstances. The legality of this situation is assessed during the consultation, and counselling is available upon request, both before and after the procedure.

If the woman is further interested in proceeding with the Medical Abortion, it is important for her to understand the possible risks:

- Bleeding – Blood loss requiring treatment is uncommon with a Medical Abortion, but severe blood loss requires hospitalisation.
- An Incomplete Abortion – occurs when there is remaining tissue within the uterus, should this occur a surgical procedure will be required.
- Infection – if this does occur, early treatment is required.
- Future Fertility is discussed after the use of Mifepristone and Misoprostol.
- Problems that may occur during & after the termination.

All relevant medical details and history are noted, and the option of a Medical TOP and Surgical Top will be discussed and given to the patient. The gestation and intra-uterine pregnancy will be confirmed with an ultrasound, and after further discussion, the Doctor will then determine if the patient is a suitable candidate.

The patient must then read and sign a consent form for the procedure of a Medical Termination, and is supplied with a 24 hour emergency contact number, should heavy bleeding or any other concerns arise.

After counselling and the pregnancy has been confirmed by the doctor, the patient is provided with a 200mg **Mifepristone** tablet to take whilst at the clinic. An anti-nausea medication of Maxalon is also provided should it be required.

The effects of Mifepristone are usually mild and do not last long, and the patient may experience nausea or mild cramping. Mifepristone changes the uterine lining, causing the pregnancy to detach. Some bleeding or spotting is also common, but it is rare for the pregnancy to abort after the Mifepristone alone.

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The drug Misoprostol is given to the patient by the doctor to take with them. There are 2(two) options in administering these 4(four) tablets. They can be inserted high vaginally or taken by dissolving them slowly between the cheek and teeth. Either of these methods is done a 36 to 48hours after taking the Mifepristone, to bring on the termination. Misoprostol causes cramping, pain and bleeding usually within one to six hours of inserting the tablets. Pain can range from mild period-like pain, to severe cramping. The patient is directed to manage the pain with relievers such as Nurofen, Naprogesic, Panadol and Panadeine. Most importantly they are instructed to use the pain relief earlier in the treatment for it to have the best effect.

The patient is advised at the time of the initial consultation that she will be contacted about 24 hours after the Misoprostol to discuss her experience and she is also required to have a follow-up appointment or (post-abortion) appointment after two weeks of commencing the termination. An ultrasound performed at the clinic will confirm if the termination is complete and has been successful. In the event of the termination not being successful, a Dilation and Curettage will be performed in the clinic.

All medical outcomes will be recorded and maintained, as well as any adverse events will be noted. These reports are then forwarded to the [redacted] six monthly, ending June and December.