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A randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation

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1 PROTOCOL CONTACTS

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2 PROTOCOL SIGNATURE PAGE

2.1 Protocol authorisation signatories

Signature …… Date ……
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Signature …… Date ……
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2.2 Chief Investigator signature

I agree to comply with the study protocol, the principles of GCP and the appropriate reporting requirements.

Signature …… Date ……
Professor Stephen Robson

3 CONTENTS

4 GLOSSARY

Abbreviation	Definition
AE	Adverse Event
GA	General Anaesthetic
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
IES	Impact of Events Scale
IMP	Investigational Medicinal Product
NHS	National Health Service
PM	Preference Medical
PS	Preference Surgical
RCOG	Royal College of Obstetricians and Gynaecologists
RM	Randomised Medical
RS	Randomised Surgical
RVI	Royal Victoria Infirmary
SAE	Serious Adverse Event
SUSAR	Serious Unexpected Suspected Adverse Reaction
TOP	Termination Of Pregnancy
WTP	Willingness To Pay

5 PROTOCOL SUMMARY

Full Title:	A randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation
Short title:	TOP study
Protocol version:	2 (incorporating protocol amendment 1)
Protocol date:	9th February 2006
Chief Investigator:	Professor Stephen Robson
Sponsor:	Department of Health, Research & Development, Health Technology Assessment Programme
Funder:	Department of Health, Research & Development, Health Technology Assessment Programme
Study design:	A partially randomised preference trial comparing surgical and medical termination of pregnancy up to 14 weeks' gestation. Follow up will be conducted at 2 weeks and 3 months
Study intervention:	Surgical or Medical Termination of pregnancy
Objectives:	To determine differences in efficacy, acceptability and cost.
Primary outcome variable:	Acceptability, determined by preferred method of a future termination.
Study site:	Royal Victoria Infirmary, Newcastle upon Tyne
Study population:	2232 eligible women
Study duration:	3 years

6 RESPONSIBILITIES

Sponsor:
Department of Health, R&D, Health Technology Assessment Programme

Trial Management:
The following functions falling under the responsibility of the sponsor will be delegated to the Newcastle Clinical Trials Unit:

- **Authorisation**; including CTA request, research ethics committee opinion, notification of protocol amendments and the end of trial
- **GCP and conduct**; including GCP arrangements, management of IMP (free of charge), emergency & safety procedures
- **Pharmacovigilance**; including defining adverse events/reactions, reporting of SUSARs, notifying investigators of SUSARs, annual listings & safety report

Trial conduct at site:
Investigator responsibilities:

- Study conduct and the welfare of study subjects
- Familiar with the use of the investigational medicinal product as described in the product information, administration according to the protocol and drug accountability
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events
- Screening and recruitment of subjects
- All trial related medical decisions
- Provision of adequate medical care in the event of an adverse event
- Obtaining site specific assessment from local ethics committee
  - Assistance will be provided by the CTU
- Obtaining R&D approval from the appropriate Trust and abide by the policies of Research Governance
- Compliance with the Principles of GCP
- Obtain written informed consent from participants prior to their participation
- Qualified by education, training and experience to assume responsibility for the proper conduct of the trial and shall provide a current signed & dated curriculum vitae as evidence
- Availability for study meetings and in the case of an audit
- Maintenance of study documentation and compliance with reporting requests
  - Maintaining a project file, including copies of study approval, list of subjects and their signed informed consent forms
  - Documenting delegation of tasks to study personnel e.g. Co-Investigators, research Nurse
  - Ensure data collected is accurate & complete
  - Updating the CTU regarding the progress of the trial
  - Ensure subject confidentiality is maintained during the project and archival period
- Ensure archival of study documentation for a minimum of 10 years following the end of the study

7 BACKGROUND

Unwanted pregnancy is a major health issue; worldwide an estimated 53 million abortions are performed each year, resulting in up to 100,000 maternal deaths [1]. In 2002 nearly 185,000 pregnancy terminations were performed in England and Wales of which 78% were funded by the NHS. The majority of abortions are performed before 13 weeks of pregnancy (87%) and by surgical methods (86%) [2]. In 2000, 64 of 194 (33%) units with facilities for termination of pregnancy before 13 weeks provided both medical and surgical methods, while among the 130 units with only one method available, surgical termination of pregnancy was the only option in 79% [3]. Prior to 14 weeks' gestation surgical termination can be performed by vacuum aspiration (VA).This procedure, performed under general anaesthesia, has been the 'method of choice' since the 1960's; VA is currently used in 81% of abortions performed prior to 10 weeks gestation and 92% of those performed at 10-12 weeks [2]. The technique is safe and efficacious; major complications (uterine perforation, pelvic sepsis and haemorrhage requiring blood transfusion) occur in 0.2%-0.9% of cases [2, 4,5]. However up to 5% of women return to hospital with post-abortion symptoms of which 50-65% require surgical evacuation for retained products [4,5]. Complication rates increase with gestation [2, 4-6] with incomplete abortion reported in up to 12% of cases ≥ 12 weeks [5]. Cervical preparation with prostaglandins facilitates cervical dilatation and reduces complications [7]. It is recommended, if the woman is under 18 years of age or at gestations > 10 weeks, using misoprostol 400 µg vaginally 3 hours prior to surgery [7].

Medical abortion using mifepristone, an anti-progesterone, and prostaglandins has been available since the 1980's. For abortions up to 63 days gestation, evidence suggests that mifepristone (200 mg orally) followed 36-48 hours later by either gemeprost (1 mg vaginally) or misoprostol (800 µg vaginally) are equally safe and effective with 95-97.5% of women achieving complete abortion [8-10]. Because of much lower costs, 72% of units use misoprostol [5]. Complete abortion rates with single dose mifepristone / misoprostol fall from 98.5% at ≤ 49 days to 96.7% at 50-63 days [10] but are much greater after 63 days [11]. For women at 49-63 days, if abortion has not occurred 4 hours after administration of misoprostol, a second dose (400 µg vaginally or orally) may be administered [7]. Between 64-91 days gestation efficacy is increased if the initial dose of misoprostol is followed by repeated doses of 400 µg [12]. However, even using up to a maximum of 5 further doses, the need for surgical evacuation increased from 0.9% at 9-10 weeks to 7.9% at 12-13 weeks [12].

A Cochrane systematic review of medical versus surgical methods of first trimester termination of pregnancy identified only 5 relevant trials, mostly with small numbers [13]. Although the authors concluded that prostaglandins alone seemed to be less effective than surgical abortion, only one trial of mifepristone/prostaglandins was included [14]. The review suggested there was inadequate evidence to comment on the acceptability and side effects of medical versus surgical abortions. A partially randomized preference trial of medical and surgical termination of pregnancy between 10-13 weeks has subsequently been reported [15]. Side effects (vomiting, diarrhoea and abdominal pain) were higher in the medical group although there was no difference in the rates of major complications up to 8 weeks.

Available evidence suggests that 17-85% of women requesting first trimester termination of pregnancy have a preference for either a medical or surgical procedure [13-16]. The most common reason cited for preferring a medical termination of pregnancy is the avoidance of surgery and/or anaesthesia [13, 17]. The large variation in reported preference rates may be explained by factors such as gestational age, prior experience and time to access the procedure [13, 16-18]. Preference for surgical termination of pregnancy appears to increase with

gestational age [14, 15]; early in pregnancy women appear to perceive the medical procedure as easier and more natural while later it is perceived as more stressful (related to concerns about pain and seeing the foetus) [16-18]. If a woman has a preference for one method she is unlikely to be enrolled in a randomised trial or she may refuse the allocated method [17]. To represent the full range of service users, randomised trials need to include preference arms.

Service users' evaluations of the care they have received are clearly important in the context of current initiatives to develop a more patient-centred NHS. Patient satisfaction with their care is the most commonly used indicator in research on patient evaluations [19], but definitions of satisfaction vary, and different measures incorporate different dimensions of the construct, such as adequacy, suitability and acceptability. A common problem with satisfaction measures is that they exhibit ceiling effects i.e. most patients report being satisfied, and distinctions between care of different quality are often not observed. This is likely to be a particular problem in areas such as termination of pregnancy, where patients are widely observed to experience a sense of relief after the procedure. Most studies of women's views about termination of pregnancy have reported procedure acceptability; typically women have been asked whether they would opt for the same method in the future or recommend the method to a friend [13, 17, 20]; data from randomised trials indicate that acceptability of both methods before 9 weeks gestation is high *(63-92%)* with *2-36%* of women randomised to surgical termination of pregnancy preferring a medical procedure in future and *22-37%* of women randomised to medical termination of pregnancy preferring a surgical termination of pregnancy [13, 15]. Where women have a preference for one method, typically ≥ *90%* would choose the same method in the future [14, 16-18, 20]. Acceptability may be lower at later gestations; in the only randomised trial of abortion methods between 10-13 weeks, more women opted for VA again than medical abortion *(79%* vs. *70%* respectively) [15]. However response rates were low *(<50%).* The results reported above are based on the 'single question with a binary outcome' approach to assessing acceptability. Such measures are simple to collect and report but provide limited information, particularly about why respondents hold the views they do. One supplementary approach is to ask respondents to rate specific features of their care thereby providing information about the reasons underlying acceptability judgements. Using a semantic differential rating scale, Henshaw et al. [14] identified that in randomised women, medical abortion rated lower on 6 of the bipolar adjectives with pain showing by far the largest difference. Vacuum aspiration was also rated less painful in women allocated according to preference.

The psychological effects of termination of pregnancy have recently been reviewed [21]. The authors concluded that termination of pregnancy rarely causes immediate or lasting negative psychological consequences in healthy women. Indeed several studies reported positive outcomes such as relief [21]. Henshaw et al. [14] performed a partially randomised preference trial of termination of pregnancy <9 weeks and found no differences in depression, anxiety or low self esteem 2 weeks after the procedure [22] nor, in a much smaller number, 2 years later [23]. Whether medical termination of pregnancy is associated with more adverse psychological consequences after 9 weeks gestation is not known.

Although many studies have reported the outcomes of first trimester termination of pregnancy very few have randomised the method of abortion, and only one has included women beyond 9 weeks of pregnancy, despite the fact this group constitutes over *40%* of termination of pregnancies [15].There is a need for a partially randomised preference trial comparing VA with current methods of medical abortion. In addition to patient acceptability the trial needs to determine the clinical and cost effectiveness of the two methods.

In 2002 a pilot randomised trial of medical versus surgical termination in women at ≥ 9 wk

gestation was commenced at the Royal Victoria Infirmary (RVI)), Newcastle upon Tyne. Women not expressing a preference for one method were randomised to medical or surgical termination of pregnancy. All women were offered follow up at 2 weeks post-procedure. Due to limited availability of the research nurse, recruitment was only possible from selected clinics.

Of 408 women at 9-13 weeks, 284 *(70%)* were suitable and agreed to participate in research of which 139 *(49%)* were prepared to be randomised to medical or surgical termination of pregnancy. Outcome data at 2 weeks was obtained in 75 *(53%)* and included emergency admission rates, psychological scales (Impact of Event scale, Hospital Anxiety and Depression Scale) and satisfaction with care. The pilot study information has been used to inform recruitment and precision calculations' for the proposed trial.

During the pilot study women were divided into 2 gestational age groups; 9-13 weeks and 14-20 weeks based on ultrasound. Methods of medical and surgical termination of pregnancy in the 9-13 week group were identical to those proposed in the present application. Psychological impact was measured using the Impact of Event Scale [IES] and Hospital Anxiety and Depression Scale (HADS). Clinical outcome was measured using blood loss (as determined by drop in haemoglobin), unplanned (emergency) admission and symptoms (pain, diarrhoea, vomiting and vaginal bleeding). A follow up visit at the Royal Victoria Infirmary was arranged for all women in the trial and key outcomes collected at this point by clinical enquiry and questionnaire. Updated data on recruitment and follow up (as at March 2004) indicated that for the 9-13 week group, data on IES at 2 weeks post procedure was available from a total of 65% of randomised women. Statistical analysis of the psychological and clinical data has not been undertaken.

There is some indication that the follow up rate (using clinic visits and selected telephone contact) is lower in the surgical arm. This could be explained by women undergoing a surgical termination of pregnancy feeling less in need of reassurance about the termination of pregnancy outcome, and therefore being less willing to attend the follow-up visit. However a 95% confidence interval for the difference in follow-up rates between arms is 2% to 31% i.e. the data is consistent with either a difference of little or of real practical importance. Telephone follow-up was only used for the latter part of the pilot study, and we anticipate that we can obtain key outcome data in all arms for a greater proportion of women in future by offering a choice by way of place and method of follow-up.

There is a clear policy impetus to understand, qualitatively, women's preferences for medical or surgical termination of pregnancy and the decision-making processes that lead both to these preferences and to encounters with health services. The personal and political sensitivities that surround termination of pregnancy are now well established, and have important consequences for research in the field. The most important of these is resistance to inquiry into decision-making and action where this may threaten the moral viability of the woman's decisions. This means although termination of pregnancy is one of the most common surgical procedures in the UK, little work has been done that will contribute to robust understanding of preferences for types of procedures, and even less qualitative work that has investigated this problem. Instead, the objective of much research in the field has been aimed at understanding decision-making on termination in relation to promoting access or reducing delays in referral to clinical services. Recently, this approach has led to an important qualitative study in the UK. In this study, Kumar *et al* [24, 25] have shown that most women prefer *not* to discuss their decision with clinicians, but prefer instead to receive information and prompt referral. Unease about discussing personal aspects of termination has also been registered amongst professionals, especially nurses and midwives (this may also explain the paucity of social science research in

the field) [26]. Factors affecting the choice of method of termination are already known to be highly complex, and organised mainly in relation to social rather than clinical factors [27]. The problem of decision-making and preferences around termination is therefore quite unlike any other arena of clinical research, especially other areas where approaches to shared decision-making have become prominent in recent years [28].

The personal and professional sensitivities around termination of pregnancy require a highly sensitive approach to research. In this trial of surgical versus medical termination, women's preferences and responses are being intensively investigated through measures of experiences of care; strength of preference; psychological outcomes; cost effectiveness; satisfaction with care; and also by clinical measures of morbidity including experience of symptoms and emergency admission.

The intensive investigation of women's experiences and preferences within the trial provides a point of departure for the qualitative sub-study. This will draw on data collected within the economic sub-study of strength of preferences, and is an optional final phase of the trial experienced by a sub-group of 32 women. Qualitative sub-studies within trials tend to be used either as initial (reconnaissance) studies to assist in decision-making about instrument design, study organisation and recruitment; or as formative process evaluations of ongoing work [29]. In the present study, we intend to take a different tack, using the qualitative investigation as a means of illuminating women's responses to (a) the experience of participating in the trial, and (b) their perspectives on the results of the economic study of strength of preference. Directly focusing on these topics will provide useful data, but will also indirectly open up earlier decision-making processes and questions of access to investigation. A key problem in qualitative studies of personally sensitive experiences and actions is that of the subject being forced to construct an account that provides a *justification* for action in the face of anticipated moral judgements by an external authority [30], this makes for bias in accounts and we have adopted an approach to study design and data collection that is explicitly intended to move the focus of subjects' accounts away from personal justification towards a wider explanatory perspective. We will do this by asking subjects to act as lay interpreters of data collected elsewhere in the study (refer to conjoint analysis, section 15), focusing on the preferences and actions of 'notional others' [31] and to use this interpretive function as a starting point for their own accounts. This approach means that its design and application do not risk confounding recruitment and retention of subjects, or other data collection, where these are already likely to be a challenge.

8 OBJECTIVES

This is a non-commercial study to determine the acceptability, efficacy and cost of medical versus surgical termination of pregnancy.

Primary objectives

To determine the acceptability of medical and surgical termination procedures as determined by their preferred method for any future TOP.

Secondary objectives

To compare experiences of care, strength of preference, psychological impact, efficacy and cost effectiveness of surgical versus medical termination.

Qualitative sub-study

The aim of the sub-study is to better understand the foundations of women's preferences and

decision-making about method of termination. The objectives are:

(a) To identify, describe and understand women's motives for joining the trial and their experiences of participation in it.

(b) To identify, describe and understand women's personal experiences of seeking termination and decision-making about method of termination.

(c) To identify, describe and understand women's perspectives on data collected on 'strength of preference' and the model developed from conjoint economic analysis.

9 STUDY DESIGN

This is a partially randomised controlled preference trial comparing two procedures for termination of pregnancy at less than 14 weeks' gestation. Termination can be performed surgically (the uterus is evacuated under general anaesthetic) or medically (tablets given to procure abortion); it is unclear which of these methods is more acceptable to women. This design ensures the inclusion of women who have a prior procedure preference (preference group) and those who do not (randomised group), and will therefore reflect the population of a normal clinical setting.

Primary outcome measures

The primary outcome variable is acceptability of the procedure at 2 weeks after the procedure; participants will be asked if they would have the same method of termination again.

Secondary outcome measures

A secondary comparison of acceptability of the procedure will also be determined at 3 months after the procedure. Additional secondary outcome variables are strength of preference for the procedure, measured after 2 weeks; experiences of care, psychological impact, efficacy and satisfaction with care, measured at 2 weeks and 3 months after the termination procedure.

Further analysis will be performed to explore the relationships between willingness to pay, satisfaction and acceptability measures.

In order to better understand women's decisions regarding termination of pregnancy the study will include a qualitative component. A conceptual model of preferences will be developed via conjoint analysis in a group of non-pregnant women, and then explored via interview in a sample of women who have participated in the trial 2 weeks after their termination procedure.

Table of events

Visit	1 (Baseline)	2	3	
Time	up to -2w	0	+ 2w	+ 3m
Inclusion/exclusion screening	x			
Written informed consent	x			
Randomisation, if applicable	x			
Reason for preference, if applicable	x			
Demography	x			
Medical history	x			
Concomitant medication	x			
Ultrasound	x			
Strength of preference	x*		x	
Termination procedure		x		
Adverse events		x	x	x
Concomitant medication		x	x	x
Acceptability			x	x
Satisfaction with care			x	x
Experience of care			x	x
Impact of Event Scale			x	x
Anxiety & Depression Scale			x	x
Quality of Life (EQ-5D)			x	x
Consent for Qualitative sub-study			x	
Qualitative interview			x	

x* only determined prior to procedure in the preference group

The study involves up to 3 hospital visits; the third visit is currently only part of normal care for those patients where it is unclear if medical abortion has been complete or who are experiencing problems. However the RCOG has recently recommended that all women should be offered a follow-up appointment within 2 weeks of abortion [7].

Alternative methods of collecting the primary and secondary outcome data will be discussed at baseline to ensure maximum follow up:

- The third visit can be performed in a community clinic (based within Sexual & Reproductive Health Services), rather than the hospital setting.
- If participants fail to attend the 2 week follow up visit, contact and data collection will be attempted by telephone or by postal questionnaire (with an option to complete the questionnaire via the internet), according to their consent. Also if agreeable, a final option of text message will be used to elicit primary outcome data; text messaging may also be used for a visit reminder.
- 3 month follow up data will be collected via postal or web-based questionnaire.

From month 10 of recruitment, 32 women (8 from each arm) will be invited to join the qualitative sub-study during the 2 week follow up contact. A convenient time will be arranged by the researcher to perform this interview.

Definition of end of study
The end of the study will be the last participant's final study contact, at 3 months follow up.

10 SUBJECT POPULATION

This is a single site study and will be conducted at the RVI in Newcastle upon Tyne; a busy NHS unit which undertakes nearly 1300 terminations a year.

2232 women requesting termination of pregnancy are required for inclusion into the study.

10.1 Inclusion criteria

- Women requesting and accepted for termination of pregnancy at less than 14 weeks' gestation (as determined by ultrasound)
- Women under 16 years of age will be approached where they are determined to be Gillick competent (by the clinical practitioner) and where a parent is present.
- Ability to give written informed consent

10.2 Exclusion criteria

- Pre-existing medical disorder which is an indication for either medical or surgical TOP.
- Non English speaking women (apart from French, Mandarin, Cantonese, Bengali, Urdu & Arabic) due to limited availability of interpreters.
- Previous participation in this trial.
- Current participation in a "drug" related trial.

Sub-study
This sample is neither intended to be statistically representative nor to be a maximum variation sample; sampling will be purposive and sequential. Every woman entering the trial in the period after 10 months recruitment will be invited to join the qualitative sub-study at two week follow-up contact. We expect a high rate of refusal to join this sub-study and of attrition amongst those who do. This means that although inclusion and exclusion criteria will be the same as those for the main trial, the sample entering the qualitative sub-study will be highly selected.

11 SUBJECT RECRUITMENT

At the time of referral, all women are provided with standard hospital information about the choices and risks of termination of pregnancy. This information leaflet explicitly states that there is no medical evidence that one method of termination is 'better' than the other and research is currently being conducted at the RVI to better inform this choice. For reasons of confidentiality the study information sheet will not be sent to women prior to their consultation visit.

The initial consultation at the unit involves acceptance for termination and discussion of choices & risks. A nurse practitioner will discuss the available options and risks of termination, and then those women eligible for the study will be approached for interest in the study. Interested women will then discuss the study in detail with a research nurse and discuss their preference options. Written study information will be provided, along with opportunity for questions and time to consider the study. Willing participants will sign a consent form along with the research nurse, and confirm their decision for randomisation or preference for a medical or surgical termination.

For those women less than 16 years of age (minor), a parent shall also have the study explained and have opportunity to ask questions. The parent will provide written consent at the same time as and in addition to the minor's consent.

Unaccompanied women of less than 16 years, or accompanied women with unsuitable representatives, will not be considered for the study.

12 STUDY INTERVENTIONS

12.1 General information

Termination of pregnancy (TOP) is the commonest gynaecological procedure. It can be performed surgically or medically as described in section 1 (Background).

Vaginal bleeding and mild abdominal pain are normal post surgical and medical procedure. Nausea, vomiting and diarrhoea may also be experienced. There is also a risk of infection. Pain relief and antibiotics are provided as part of normal care [7]. Occasionally abortion is incomplete and surgical evacuation is required. Major complications of surgical termination are rare, but include uterine perforation, pelvic sepsis and haemorrhage.

Misoprostol is widely used in the UK to induce medical abortion and in cervical preparation for surgical termination, even though this is an unlicensed indication. Therefore for the purposes of this study misoprostol will be treated as an investigational medicinal product (IMP).

The Summary of Product Characteristics for mifepristone is included in the appendices. This will be prescribed and administered as per normal practice.

12.2 Use within the study

Misoprostol will be presented as 200µg tablets; packaged and labelled as an IMP.

Surgical termination

Women will be admitted to the Surgical Day Unit where they will receive misoprostol 400µg vaginally 3 hours prior to the estimated time of surgery [7]. Following induction of general anaesthesia and mechanical dilatation of the cervix, the uterus will be evacuated using vacuum aspiration with a 9-12 mm curette.

In the absence of excessive bleeding or other problems, women will be discharged 1-2 hours after the procedure.

In line with RCOG recommendations [7], surgical termination will only be performed after 6 weeks' gestation because of the high failure rate (relative risk 2.9 at very early gestations). The appointment for surgical termination will be timed in line with this recommendation.

Medical termination

At an initial appointment participants will be given mifepristone 200mg orally on the Gynaecological ward by the nursing staff. After 36-48 hours, they will be admitted to the Gynaecological ward where they will receive misoprostol 800µg vaginally at approximately 8:30 a.m.

Following administration of misoprostol, participants will receive oral paracetamol (500mg) plus dihydrocodeine (10mg) or diclofenac (75mg), or parental diamorphine (5mg) as required and as per normal practice.

At the time of the termination participants will receive rectal metronidazole (1g), followed by oral doxycycline (200mg) daily for 7 days, commencing on the day of the termination.

In the absence of excessive bleeding, participants will be discharged 1-2 hours after passage of the uterine contents.

Subsequent management will depend on gestation period:

Less than 9 weeks

- If the contents of the uterus have not been passed 4 hours after misoprostol administration,

a second dose of misoprostol (400µg) will be administered vaginally or orally (depending on preference and amount of bleeding) [7].

- Subsequently, if abortion does not occur and bleeding is not excessive, women will be routinely discharged between 4:30 & 5:00 p.m. The abortion occurs at home and women return for follow-up after 2 weeks.

9 to 13 weeks

- If the contents of the uterus have not been passed 3 hours after misoprostol adminstration, further doses of misoprostol (400µg) will be given vaginally (or orally if bleeding is heavy) at 3 hour intervals up to a maximum of 4 further doses [7].
- If the contents are still not passed, an ultrasound scan will be performed. In cases of an ongoing pregnancy, missed or incomplete abortion, surgical evacuation will be performed.

13 RANDOMISATION

Participants with a procedure preference will decide whether to opt for a medical or surgical termination.

Participants with no preference, and willing to be allocated a procedure at random, will be randomised using a computer system with web-based access for trial personnel (PowerTrial). Randomisation will be stratified according to gestation (less than 9 weeks and between 9 & 13 weeks) and for previous termination of pregnancy.

14 STUDY DATA

14.1 Data collection

Baseline demographic data, including medical history and method of any previous termination, education level, occupation and income will be collected by the nurse practitioner or research nurse for all participants. Contact details (including where possible mobile phone numbers) and availability will also be collected.

Those expressing a procedure preference at baseline will be asked to nominate one or more reasons from a list of eight, developed as part of the pilot trial:

1. General anaesthetic (GA) - want to be asleep (PS)
2. Fear of GA or desire to be awake and in control (PM)
3. Fetus - do not want to see fetus (PS)
4. Pain - perceived medical as more painful (PS)
5. Visits to hospital - wanted minimum (PS)
6. Duration of procedure - less time in hospital (PS)
7. Previous experience (i.e. had prior TOP) - PM or PS
8. Other (<5% of responses)

All participants will be invited to return for an out-patient (hospital or community clinic) assessment 2 weeks after the procedure. Outcome data will be collected at 2 weeks (by interview and questionnaire) and at 3 months (by questionnaire) after the procedure. For women who do not attend their visit for 2 week follow up, collection of outcome data will be attempted where previously agreed via telephone interview, mobile text message & postal or web-based questionnaire. All visits and telephone interviews will be conducted by a research nurse.

Acceptability - This will be determined at 2 weeks and 3 months after the procedure by responses to the closed question ‘If you ever have another termination of pregnancy, would you opt for the same method?’. This simple question has been used in previous preference

trials of TOP [14, 15] and can, if necessary, be easily determined by phone, questionnaire or text message.

Strength of preference - To measure women's strength of preference for medical or surgical termination we will measure willingness to pay. This technique is being increasingly used in health technology assessment [32] and has been used previously for assessing strength of preference for abortion method [23, 33]. Interviews will be conducted, using the payment card method [34], in all women in the preference arm prior to the procedure where they will be asked to state their maximum 'willingness to pay' amount for the termination method they have chosen. Interviews will also be conducted on all women in both the randomised and preference arms at 2 weeks after the procedure when they will be asked to state their maximum 'willingness to pay' amount to receive their preferred option at a future date. The validity of women's responses will be tested by examining the correlation between stated 'willingness to pay' and level of income.

Satisfaction with care - The methodological pitfalls of measuring satisfaction with care have been reviewed recently [35]. Women will be asked to rate the quality of care during the termination and the counselling and support afterwards using a 5 point Likert scale (from excellent to poor) at 2 weeks and 3 months after the procedure. Measures in which patients are asked to rate the quality of aspects of their care show greater response variability than measures which seek direct ratings of satisfaction [36] and are better predictors of whether patients will return to the same doctor in the future [36]. For analysis we will distinguish those who rate their care as excellent from the remainder as this provides better discrimination [37]. A similar assessment has been used in our pilot trial. Ratings of care will be supplemented by information on satisfaction with care from the qualitative study.

Experience of care - To provide information about the reasons underlying acceptability judgements, we will use a semantic differential rating technique administered at 2 weeks and 3 months post procedure. This instrument uses a pair of opposite adjectives (for example painless-painful) as endpoints on a graphic Likert scale. Women will be asked to indicate their experience by placing a mark on the scale. Twelve bipolar adjectives will be used, scored along an evaluation dimension representing a positive or negative attitude ranging from 3 to -3. Rating scores are quick and easy to complete and have been used previously to measure attitude towards termination of pregnancy [14,38].

We plan to undertake a further analysis to explore the relationships between willingness to pay, satisfaction and acceptability measures.

Distress, anxiety and depression - Distress will be measured using the IES at 2 weeks and 3 months after the procedure. This 15 item scale measures subjective distress to a specific event (in this case termination of pregnancy) [39] and is the most likely to pick up a difference in actual experience of having one procedure rather than another. Two subscales measure intrusion and avoidance and both are likely to arise differently from the procedures under comparison. Anxiety and depression will be measured using the HADS at 2 weeks and 3 months after the procedure. This is a widely used 14 item self report scale designed for medical patients [40]. Depression is the main problem service providers have been concerned about [21]. Both the IES and HADS have been used in women after termination of pregnancy [21-23] and in our pilot study.

Quality of Life (EQ-5D) – This is a six itemed validated questionnaire developed by a European committee to provide a preference-based measure of quality of life, needed for the economic evaluation [41].

Emergency admission - Efficacy will be determined by comparing the rates of emergency admission (on the day of the procedure or after discharge) at 2 weeks and 3 months after the procedure. All women will be questioned about adverse events at the 2 week and 3 month follow up to ensure that data is also captured for admissions or visits to another hospital or their GP. The rationale for choosing this outcome is that it is likely to include all women with significant procedure-related morbidity due to (a) incomplete abortion, missed abortion or ongoing pregnancy (all of which require surgical evacuation) and (b) pelvic infection without retained products of conception. Further there is evidence to suggest that women experiencing a failed termination (requiring surgical evacuation) or excessive pain and/or bleeding (resulting in admission) are more likely to classify the experience as unsatisfactory [42] and to opt not to have the same procedure again in the future [20, 42].

Frequency and extent of symptoms - The incidence of nausea, vomiting, diarrhoea, dizziness and abdominal pain on the day of the procedure will be recorded as well as an assessment of the severity of pain (using a 10 cm visual analogue scale) and analgesic use. Symptoms after discharge will be ascertained at the 2 week follow up visit by the research nurse. Specifically the duration and severity of vaginal bleeding and pain as well as the length of time taken off work and to return to normal activity will be recorded [15].

Concomitant medications will be recorded at baseline and at the time of the termination procedure by abstraction from the medical notes. Women will be asked about concomitant medications at 2 week follow up.

Sub-study
Semi-structured interviews: 32 participants will be invited to take part in one semi-structured interview with a trained interviewer. The highly selected nature of the sample, and the topic sensitivity, mean that decision-making and experiences of termination will be their indirect rather than direct focus. Interviews will be of up to 90 minutes duration and will be divided into two discrete sections.

In part 1 women will be asked about general issues connected with their experience of entering and participating in the trial, and their understanding of its design and methods. This part of the interview will indirectly elicit accounts of their experience of referral pathways into the service and trial, specific accounts of their experiences of termination, and its outcome.

In part 2 the interviewer will describe and demonstrate outcomes of a conjoint analysis (refer to section 15) using structured questions and flashcards. Subjects will be invited to comment on the model derived from conjoint analysis from the perspective of a ‘notional other’ [31], and will also be asked about the ‘fit’ between the ‘willingness to pay’ model and their own experiences.

With the consent of the participant, each interview will be audio-recorded using an unobtrusive mini-disk recorder and conference microphone, and later transcribed. Where participants do not consent to recording, handwritten notes will be made.

14.2 Data handling

Study data collected will be entered directly, where possible, to avoid transcription errors, into a web-based PowerTrial data capture system by the research nurse, or participant for the web-based questionnaires. The remaining study data will be entered from paper source. Audit trail and full daily back-up will be provided.

Data will be collected to standards required by CFR Title 21, part 11, and EU Directive

2001/20/EC, and adhere to the Data Protection Act 1998.

The quality and retention of study data will be the responsibility of the Newcastle Clinical Trials Unit. All study data will be archived in line with Trust policy (currently 10 years).

15 STATISTICAL CONSIDERATIONS

15.1 Statistical analysis

The analysis strategy will be similar to that used in a partially randomised preference trial of treatment for depression [43]. The trial will contain 4 intervention groups:

1 randomised to medical termination (RM)

2 randomised to surgical termination (RS)

3 preference for medical termination (PM)

4 preference for surgical termination (PS)

The analysis will be on an intention to treat basis (although it is anticipated that women will always get the randomised or preferred intervention). Those in either medical arm (RM or PM) who subsequently receive surgical intervention, due to incomplete or missed abortion, will be analysed as per the assigned medical arm.

Baseline variables - Although randomisation should balance out baseline characteristics, it will be important to compare these in the four groups to see if those who are prepared to be randomised differ from those who have a preference. If so, there are problems in extrapolating any conclusions from the randomised arms to the general population.

Primary analysis

Main comparison of randomised arms:

a. Comparison of proportions of women finding the procedure acceptable. We will also investigate the interaction between past history of TOP and intervention group on acceptability and gestational age (as a continuous variable) and intervention group on acceptability
b. Comparison of mean values on psychological and rating scales.
c. Comparison of proportions of women rating care as 'excellent'
d. Comparison of WTP between those women in the two randomised groups.

Secondary analysis

Secondary comparison of medical and surgical arms (preference and randomised subgroups combined):

a. Comparison of proportions of women finding the procedure acceptable and rating the quality of care as 'excellent' - the comparison will adjust for key baseline variables using logistic regression. We will also investigate the interaction between past history of TOP and intervention group on acceptability, and gestational age (as a continuous variable) and intervention group on acceptability.
b. Comparison of mean values of psychological and rating scales - the comparison will adjust for key baseline variables using multiple regression.
c. Comparison of proportions of women with emergency admission and particular symptoms - the comparison will adjust for key baseline variables using logistic regression.
d. Comparison of WTP between those women in the combined groups.

Tertiary comparison of combined preference and randomised groups:

The aim of this comparison is to determine if receiving a preferred intervention improves key outcomes. Comparisons will be of acceptability, psychological and rating scales with methods as for secondary comparisons.

Cost effectiveness analysis:
Cost data relating NHS resource use (in both primary and secondary care) will be collected following established methods [44] up to 3 months post-termination for both surgical and medical interventions. This will include data relating to the initial procedure, hospital stay, follow up care as inpatients, any additional interventions and out-patient appointments. Data relating to GP consultations specifically for follow up care relating to the TOP will be collected using the postal questionnaire at 3 months and, if agreed previously, by telephone where this is not returned. Data relating to secondary and primary follow up care and any interventions required will be used to compare the burden placed on patient own resources when using either medical or surgical termination. The cost-effectiveness analysis will be expressed as the cost per successfully completed termination. Extensive one-way and multivariate sensitivity analysis will be undertaken in the analysis of the final results [45].

Clinical effectiveness analysis:
Previous studies have used a variety of measures of clinical effectiveness but emphasis has been placed on failed TOP (with an ongoing viable pregnancy), incomplete abortion and presumed pelvic infection. Based on our proposed sample size, the precision with which we could detect differences in each of these complications is limited. Hence we have opted to use a combined measure of effectiveness which captures unplanned time spent in hospital, a key outcome for women.

Our definition of 'emergency admission' includes;

1. Unplanned overnight stay on the day of termination
2. Emergency hospital assessment or admission after discharge

All cases of incomplete abortion, missed abortion, ongoing pregnancy (all of which require surgical evacuation) and pelvic infection without retained products of conception will therefore be included in this outcome. A very small number of women may be admitted to other units but we would anticipate collecting clinical outcome data from their hospital discharge summary and/or via our follow up.

Qualitative sub-study
Conjoint analysis or discrete choice experiment (DCE):
In order to identify the key factors that shape women's preferences for termination services we will conduct a discrete choice experiment. This technique measures the strength of individual's preferences for the various attributes of a clinical intervention [46] and has been successfully used in research relating to the provision of services for women [47]. Interviews will be conducted with a sample of 100 non-pregnant women recruited from local Contraception / Sexual Health clinics. Women will first be asked if they are interested in participating in a research interview, before provision of an information sheet, an informed discussion and written consent. These interviews will begin prior to recruitment for the main study. Previous research suggests this sample size should be adequate to provide precise parameter estimates with the number of attributes and choices we will use [48]. This sampling frame has been chosen to reduce the data collection burden on the trial sample and to avoid interference with women in the trial forming and stating preferences.

Qualitative analysis:
We will use a model of preference developed from the discrete choice experiment as the basis for a semi-structured interview with 32 women (8 from each of the four groups: preference

surgical, preference medical, randomised surgical and randomised medical). A conventional model of qualitative analysis will be used [49]. The analytic product of this work will be (1) a comparative model of preferences and their normative constraints and (2) a model of contextual features that affect decision-making about termination of pregnancy.

Interview transcripts will form the formal data for analysis. Following the conventional model of constant comparative analysis of transcribed data set [49], transcripts will be interpreted iteratively, developing themes (or categories) within respondents' discourse. To facilitate qualitative analysis, and to provide an audit trail for governance purposes, we will use QSR software to manage data transcripts, coding and memo'ing. Initial thematic analysis will be conducted by the qualitative researcher. Transcripts will be searched for common themes and deviant cases (in relation to part 1 of the interview). Themes will be indexed (as 'codes') and searches for discrete instances of codeable items of speech will be undertaken in both cumulative comparisons (i.e. between interviews in the same arm of the trial) and condition comparisons (i.e. across interviews gathered from different arms of the trial). This will provide a robust account of the common themes relating to women's responses of joining and participating in the trial, and these themes (and deviant cases) will be recorded in a simple frame [50]. Because part 2 of each interview will involve some structured questions (and flashcards showing simple histograms of quantitative data), direct thematic comparisons will be made across a range of responses, and some simple quantification of results will also be possible. Once initial analysis have been undertaken by the qualitative researcher, qualitative inter-rater checking will be undertaken on a sample of cumulative and condition comparisons. This will add value to analysis [51] and will enable secure claims about the quality of data to be made.

15.2 Sample size calculation

The power of the study is based on the main comparison of acceptability between women randomised to medical or surgical TOP. Assuming the acceptability of medical termination to be 75%, we would need responses from 335 women in each randomised arm to detect a difference in acceptability of 10% (i.e. from 75% to 85%) with a significance level of 5% and power of 90%. We believe this difference in the level of acceptability is important for both consumers and providers; a similar difference was employed by Ashok et al [15] in their large randomised comparison of abortion methods.

Based on the power calculation we need primary outcome data on 670 women randomised to medical or surgical TOP at <14 weeks' gestation. In order to achieve this number we calculated;

1. 1116 women need to be randomised (assuming 40% of women randomised fail to attend for follow up and primary outcome data is therefore not available).
2. 2232 women need to be recruited (assuming 50% of women agreeing to participate in the study have a preference for medical or surgical TOP and are therefore not suitable for randomisation).
3. **3188** women need to be approached (assuming 30% of women accepted for TOP will decline involvement in the study).

Justification for assumptions – All three assumptions were based on our experience from an earlier pilot trial conducted at the RVI involving women requesting TOP at 9-13 weeks' gestation. For reasons detailed in [25] we believe our assumption of 60% follow up is conservative. Further, previous trials conducted in the UK have reported that 54% [14] and 82% [15] of recruited women undergoing TOP at < 9 weeks and 9-13 weeks respectively were prepared to have their method of TOP determined by randomisation. Thus our estimate of 50%

may also be conservative. The proportions of women accepted for TOP who agreed to join these 2 randomised preference trials were not reported. Data from non-randomised studies conducted in the UK suggest 87-93% of similar women are prepared to participate in studies involving follow up (including psychological questionnaires) after TOP, suggesting our assumption of 70% (based on the pilot study) is realistic.

16 COMPLIANCE AND WITHDRAWAL

In order to increase the proportion of participants returning for follow up after 2 weeks, an option to attend a community clinic has been incorporated in the design. Thus, allowing ease of access and evening appointments.

A range of contact processes are also included to maximise capture of primary and secondary data where participants fail to attend the week 2 follow up visit. These include telephone contact (up to three attempts), postal questionnaires (up to two attempts), or a web-based questionnaire option, to capture the primary variable. For agreeable participants text messaging will be used for a visit reminder at week 2 and collection of the primary variable (up to two attempts).

Following reasonable attempts to capture data and non-response, participants will be considered lost to follow-up.

Participants who withdraw their consent following the procedure will not be replaced.

17 DATA MONITORING

17.1 Discontinuation rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Trial Steering Committee (see below), regulatory authority or ethics committee concerned.

17.2 Monitoring, quality control and assurance

The trial will be managed through the Clinical Trials Unit (CTU), University of Newcastle in accordance with the EU Trials Directive, the Research Governance Framework for Health and Social Care and MRC Guidelines for Good Clinical Practice in Clinical Trials. Prof. S. Robson will have overall responsibility for the day to day conduct of the trial supported by the nurse coordinator, CTU Trial Manager and Trial Management group (TMG). The TMG will include the principle investigators, co-applicants and nurse representation.

The Trial Steering Committee (TSC) will be chaired by Professor Alan Templeton, University of Aberdeen, to include two other independent members and two lay members. It is proposed the TSC will meet twice during the first year of the trial and then annually. Their role is to monitor and supervise the trial, to ensure it is conducted to high standards in accordance with the protocol, the principles of GCP, and with regard to patient safety.

The Trial Manager will ensure that the study is conducted in accordance with GCP through a combination of central monitoring and site monitoring visits.

Central monitoring

- all documentation essential for study initiation will be reviewed prior to site authorisation

Site monitoring

- Consent forms will be reviewed as part of the study file and the presence of a copy in

medical records confirmed
- Consent forms will be compared against the study participant identification list
- Inclusion/exclusion criteria will be reviewed for 20% of participants
- Serious adverse events will be verified against medical records
- The presence of essential documents in the study file will be checked
- Management of the IMP will be reviewed periodically

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

A final site visit will be performed at the end of the study
- To complete final monitoring requirements, as above
- To review archiving of study site documentation

18 PHARMACOVIGILANCE

18.1 Definitions

An 'adverse event' (AE) is any untoward medical occurrence which does not necessarily have a causal relationship with the treatment.

A 'serious adverse event' (SAE) is any untoward medical occurrence or effect that at any dose
- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- results in persistent or significant disability or incapacity.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement should be exercised in deciding whether an adverse event or reaction is serious in other situations. Important adverse events or reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

An 'adverse reaction' is an untoward or unintended response to an investigational medicinal product (IMP) related to any dose administered.

A 'suspected unexpected serious adverse reaction' (SUSAR) is a severe adverse reaction, the nature of which is not consistent with the applicable product information.

18.2 Expected adverse reactions

18.2.1 Expected side effects of the termination procedure

Some degree of abdominal pain and vaginal bleeding is expected during and after a medical or surgical termination of pregnancy. Major complications are uterine perforation, pelvic sepsis and haemorrhage (requiring blood transfusion).

18.2.2 Expected adverse reactions to misoprostol

Misoprostol may cause diarrhoea, abdominal pain, nausea, vomiting, headache, dizziness and, more rarely, chills and fever.

Uterine bleeding, sometimes heavy and prolonged, may occur.

Very frequent uterine contractions are observed in the hours following prostaglandin intake.

18.2.3 Expected adverse reactions to mifepristone

Refer to appendix A, Summary of Product Characteristics.

18.3 Protocol specifications

For the purposes of this protocol all non-serious adverse drug reactions and serious adverse events will be recorded.

The incidence of nausea, vomiting, diarrhoea, dizziness, abdominal pain and bleeding will be recorded following explicit questioning, all other adverse drug reactions will be recorded as AEs.

The following are expected serious adverse events which are being explicitly recorded during the study: emergency admissions for incomplete abortion, missed abortion, or ongoing pregnancy (all of which require surgical evacuation) and pelvic infection without retained products of conception. These events will not be considered SAEs for reporting purposes, as described below.

18.4 Reporting serious adverse events

All Serious Adverse Events, as specified by the protocol above, shall be reported to the Newcastle Clinical Trial's Unit immediately by fax or email:

The initial report must contain the following minimum information:

1. Study identifier
2. Subject's unique study number
3. Age
4. Event description
5. Start date of event
6. Reason for seriousness i.e. death, life-threatening, hospitalisation, disability/incapacity or other
7. Date of termination procedure
8. Causality to procedure (medical or surgical) or mifepristone or misoprostol
9. Reporters name & date

The follow up report must contain all of the above, plus:

1. Gender
2. Stop date of event
3. Mifepristone & misoprostol (dose, route, duration dates)
4. Concomitant medication (name, dose, route, duration dates, indication)
5. Outcome, including diagnosis
6. Reporters name & date

The Clinical Trials Unit must report all SAEs which are also unexpected adverse drug reactions to the regulatory authority and ethics committee concerned within 15 days (7 days if life-threatening or resulting in death). Therefore it is very important that the initial report is faxed or emailed to the Clinical Trials Unit within 24 hours of discovery.

19 ETHICAL CONSIDERATIONS

Prior to commencement of the trial, a Clinical Trial Authorisation will be obtained from the MHRA, favourable opinions will be sought from the Research Ethics Committee and Trust R&D.

Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures.

Non-English speaking subjects will be included where possible: as part of the NHS service interpreters are provided at the initial consultation; and translation of the information sheet will be provided in 6 additional languages (choice of languages based on demand for translation services at the RVI).

20 FINANCE AND INSURANCE

The NHS Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial.

The NHS R&D Health Technology Assessment programme is funding this study. The Newcastle Primary Care Trust are providing additional funds to support the community clinics used for follow-up visits.

21 STUDY REPORTING

Results of the study will be reported to the HTA, and be available on their web site.

Participants may have access to the results on request.

All data collected during the study, and any intellectual property arising from the use of those data, shall be owned by the University of Newcastle.

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23 APPENDICES

A: Mifepristone, Summary of Product Characteristics

B: Willingness to Pay

C: Satisfaction with care

D: Experience of care

E: Impact of Event Scale

F: Hospital Anxiety and Depression Scale

G: Quality of Life Questionnaire

H: Summary of changes to Protocol Version 1 (09FEB2005)

Appendix A: Mifepristone Summary of Product Characteristics

Exelgyn Laboratoires

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75008 Paris
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Telephone:	**+44 (0)1491 642 137**
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Medical Information direct line:	**+44 (0)800 7316 120 Freephone**
Medical Information e-mail:	**exelgyn.uk@btinternet.com**
Medical Information facsimile:	**+44 (0)800 7316 120**

Document last updated on the *e*MC: **Tue 04 December 2001**

Mifegyne

1. NAME OF THE MEDICINAL PRODUCT

Mifegyne

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: Active Ingredient – Mifepristone 200mg

3. PHARMACEUTICAL FORM

Light yellow, cylindrical, bi-convex tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

(1) Medical termination of intra uterine pregnancy of up to 63 days gestation.
(2) Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination.
(3) For use in combination with gemeprost for termination of pregnancy between 13 and 24 weeks gestation.
(4) Labour induction in fetal death in utero
For termination of pregnancy mifepristone may only be administered **in accordance with the Abortion Act 1967 as amended by The Human Fertilisation and Embryology Act 1990.**
As a consequence, when used for termination of pregnancy, mifepristone and any treatment necessary to effect complete termination of the pregnancy can only be prescribed by a medical doctor and administered in a NHS or non NHS hospital or centre (having approval to undertake termination of pregnancy). The product will be administered under the supervision of a medical practitioner.

4.2 Posology and method of administration

(1) Therapeutic termination of pregnancy of up to 63 days gestation.
600mg of mifepristone (3x200mg tablets) by mouth in a single dose. The dosage is independent of body weight.
Unless abortion has already been completed, gemeprost 1.0mg p.v should be given 36 – 48 hour later in the treatment centre.

(2) Softening and dilatation of the cervix
600mg mifepristone by mouth 36-48 hours prior to the planned operative procedure.
(3) For use in combination with gemeprost for termination of pregnancy between 13 – 24 weeks gestation
600mg mifepristone (3x200mg tablets) is taken by mouth 36-48 prior to scheduled prostaglandin termination of pregnancy
The patient must return to the treatment centre 36-48 hours later, the recommended procedure for therapeutic termination of pregnancy with gemeprost **must** then be followed. ***See gemeprost SPC***
(4) Labour induction for fetal death in utero
600 mg of mifepristone (200mg x 3 tablets) in a single oral daily dose for two consecutive days.
Labour should be induced by the usual methods if it has not started within 72 hours following the first administration of mifepristone.
If the patient vomits shortly after administration of the mifepristone she should inform the doctor.

4.3 Contraindications

Suspected ectopic pregnancy
Pregnancy not confirmed by ultrasound scan or biological tests
Chronic adrenal failure
Severe Asthma not controlled by therapy
Known allergy to mifepristone or any component of the product
Inherited porphyria
If gemeprost is used, any contraindication to gemeprost (see gemeprost product information).

4.4 Special warnings and special precautions for use

WARNINGS
In the absence of specific studies, mifepristone is not recommended in patients with:
Renal failure, hepatic failure or malnutrition.
Patients with prosthetic heart valves or who have had one previous episode of infective endocarditis should receive chemoprophylaxis according to the current UK recommendations.
1) Medical termination of pregnancy of up to 63 days gestation
The method requires active involvement of the woman who should be informed of the requirements of the methods:
- the necessity to combine treatment with prostaglandin to be administered at a second visit.
- The need for a follow up visit within 10 to 14 days after intake of mifepristone to check that abortion is complete.
- The possibility of failure of the method which may require termination by another method.
In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of mifepristone.
The expulsion may take place before prostaglandin administration (in about 3% of cases). This does not preclude the follow up visit to check that the abortion is complete.
-Risks related to the method
- Failures
The non-negligible risk of failure, makes the follow up visit mandatory to check that abortion is complete.
- Bleeding
The patient must be informed of the occurrence of prolonged vaginal bleeding (up to 12 days after intake of mifepristone) which may be heavy. Bleeding occurs in almost all cases and it not in any way proof of complete expulsion.

The patient should receive precise instructions on whom she should contact and where to go in the event of any problems, particularly in the case of very heavy vaginal bleeding**.**
A follow-up visit must take place within a period of 10 to 14 days after administration of mifepristone to verify by the appropriate means (clinical examination, ultrasound scan, and Beta-HCG measurement) that expulsion has been completed and that vaginal bleeding has stopped or substantially reduced. In case of persistent bleeding beyond the control visit, its disappearance should be checked within a few days.
If continuing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.
Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.
In the event of continuing pregnancy diagnosed after the control visit, termination by another method will be proposed to the woman.
Since heavy bleeding requiring hemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemostatic disorders with hypocoagulability, or with anemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anaemia.

2) Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of Mifepristone must be followed 36 to 48 hours later and not beyond, by surgical termination.

-Risks related to the method

- Bleeding

The woman will be informed of the risk of vaginal bleeding which may be heavy, following intake of mifepristone. She should be informed of the risk of abortion prior to surgery (although minimal): she will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.

Other risks

They are those of the surgical procedure.

3) For use with gemeprost for termination of pregnancy between 13 – 24 weeks.

For the full efficacy of therapy, Mifepristone must be followed, 36 to 48 hours later by initiation of gemeprost.

-Risks related to the method

- Bleeding

The woman will be informed of the risk of vaginal bleeding following intake of mifepristone. She should be informed of the risk of abortion prior to administration of gemeprost (although minimal): she will be informed on where to go in case of emergency.

Other risks

They are those of gemeprost administration.
A follow-up visit is recommended at an appropriate interval after delivery of the fetus to verify that vaginal bleeding has stopped or has substantially reduced. Persistence of vaginal bleeding could signify incomplete abortion and appropriate investigation/treatment should be considered.

4) In all instances

The use of mifepristone requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.
During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.
To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

PRECAUTIONS

1) In all instances

In case of suspected acute adrenal failure, dexamethasone administration is

recommended. 1 mg of dexamethasone antagonises a dose of 400 mg of mifepristone.
Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.
A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Use non-NSAI analgesics.

2) Medical termination of intra-uterine pregnancy with mifepristone and gemeprost

Rare serious cardiovascular accidents have been reported following the intra muscular administration of the prostaglandin analogue sulprostone (withdrawn in 1992). No such cases have been reported since analogues of PGE_1 (gemeprost or misoprostol) have been used. For these reasons and as a special precautionary measure, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

Method of prostaglandin administration

During administration and for a minimum of three hours following administration and in accordance with clinical judgement, the patients should be monitored in the treatment centre, which must be equipped with the appropriate equipment.

3) For the sequential use of mifepristone - prostaglandin, whatever the indication

The precautions related to the prostaglandin used should be followed where relevant.
The treatment procedure should be fully explained and completely understood by the patient. There is a Patient Information Leaflet available for each of the indications in the tablet carton. Prior to administration of mifepristone the appropriate leaflet should be given to the patient to read.

4.5 Interaction with other medicinal products and other forms of Interaction

In view of the single dose administration, no specific interactions have been studied. However, there could be interactions with drugs which modulate or inhibit prostaglandin synthesis and metabolism. See PRECAUTIONS above.

4.6 Pregnancy and lactation

In animals (see section 5.3 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.
With subabortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone.
In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whetherthe molecule is a human teratogen.
Consequently:
- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, the control visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the control visit (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, careful ultra-sonographic monitoring of the pregnancy should be carried out.

Lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be

avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Most frequently reported undesirable effects (mifepristone)

• Urogenital

- Bleeding

Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 0.7% of cases.

- Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
- During induction of second trimester termination of uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.

• Gastrointestinal

- Cramping, light or moderate.
- Nausea, vomiting.

Other undesirable effects (mifepristone)

• Hypersensitivity and skin

- Hypersensitivity: skin rashes uncommon (0.2%), single cases of urticaria.
- Single cases of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

• **Other systems**

- Rare cases of headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

Undesirable effects (gemeprost)

- nausea, vomiting or diarrhoea, and rarely hypotension (0.25%)

4.9 Overdose

Tolerance studies have shown that administration of doses of mifepristone of up to 2g caused no unwanted reactions. Nevertheless, in the event of massive ingestion signs of adrenal failure might occur. Any suggestion of acute intoxication, therefore, requires treatment in a specialist environment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins.

Mifepristone induces softening and dilatation of the cervix, softening and dilatation has been shown to be detectable from 24 hours after administration of mifepristone and increases to a maximum at approximately 36 – 48 hours after administration.

In the majority of cases, abortion will occur within 4 hours of administration of gemeprost.

During the termination of pregnancy between 13 and 20 weeks gestation, mifepristone

administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the dose of gemeprost required for the expulsion.
Mifepristone binds to the glucocorticoid receptor**.** In animals at doses of 10 to 25 mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.
Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

5.2 Pharmacokinetic properties

After oral administration of a single dose of 600 mg mifepristone is rapidly absorbed. The peak concentration of 1.98 mg/l is reached after 1.30 hours (means of 10 subjects). There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.
After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.
In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.
N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.
Mifepristone is mainly excreted in faeces. After administration of a 600 mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal silica 3mg, Maize Starch 102mg, Povidone 12mg, Microcrystaline cellulose 30mg, Magnesium Stearate 3mg.

6.2 Incompatibilities

None known.

6.3 Shelf life

Tablets - 36 months.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Blister pack (PVC and Aluminum foil and carton) containing 3 tablets.

6.6 Instructions for use and handling

The treatment procedure should be fully explained and completely understood by the

patient.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Exelgyn S.A., 6 rue Christophe Colomb, 75008 Paris, France

8. MARKETING AUTHORISATION NUMBER(S)

Mifegyne Tablets 16152/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Renewal May 1999

10. DATE OF REVISION OF THE TEXT

August 2001

Appendix B: Willingness to Pay

Methods and Questions

Women will be asked to state their WTP for their preferred method of termination at the following points

1. Pre TOP – for women expressing a preference and enrolled in the 'preference arm' we will ascertain the maximum amount WTP using the payment card method

2. Post TOP – all women who underwent TOP will be asked which method they would choose if undergoing a future TOP and IF they would be WTP an amount to receive that preferred option at a future date. If they answer 'yes' to this we will ascertain the maximum amount WTP using the payment card method

Questioning strategy (outline)

Description of termination method
Choice of termination method
Willing to pay?

1 If No – asked why not
2 If Yes – payment card method used (see below)

Then asked to explain the amount indicated (NB there is a need to categorise protest zeros from non-demanders)

Payment Card Method

The concept of willingness to pay and the payment card method have been used previously in a study of women's preferences in the termination of pregnancy [52].

In this study once respondents have indicated if they have a preference for a particular method of termination and that they would be willing to pay to access that method they will be handed a card containing a list of values from £0 to £1000 and £1000 plus.

£0 £60 £140 £300 £800£5 £70 £160 £350 £900£10 £80 £180 £400 £1000£20 £90 £200 £450 £1000+£30 £100 £225 £500£40 £110 £250 £600£50 £120 £275 £700 £1000
If £1000+, can you say what is the exact amount?

Respondents will be asked to put a cross by the amounts that they would definitely not pay and then to consider what would be the maximum amount that they would be willing to pay by circling the relevant value. If respondents indicate '£1000 plus' they will asked to write in the amount. All respondents will be asked an open ended question regarding why they chose the amount indicated.

Other data to be collected:
Income, age, age at which left education, occupation, previous operation with a general anaesthetic (yes/no)

Appendix C: Satisfaction with care

The E5 satisfaction measure assesses satisfaction with the,

1) procedure overall

2) technical quality (thoroughness, carefulness, competence)

3) interpersonal manner (courtesy, respect, sensitivity, friendliness) of the staff

4) length of wait from request to procedure

Using a five-choice evaluation scale,

excellent	very good	good	fair	poor

Appendix D: Experience of care

Semantic differential rating for acceptability of procedure

painless	3	2	1	0	1	2	-3	painful
happy	3	2	1	0	1	2	-3	sad
good	3	2	1	0	1	2	-3	bad
pleasant	3	2	1	0	1	2	-3	unpleasant
positive	3	2	1	0	1	2	-3	negative
safe	3	2	1	0	1	2	-3	dangerous
attractive	3	2	1	0	1	2	-3	unattractive
mild	3	2	1	0	1	2	-3	harsh
agreeable	3	2	1	0	1	2	-3	disagreeable
active	3	2	1	0	1	2	-3	passive
easy	3	2	1	0	1	2	-3	hard
fast	3	2	1	0	1	2	-3	slow

Appendix E: Impact of Event Scale

Below is a list of comments made by people after stressful life events. Using the following scale, please indicate (with a …) how frequently each of these comments were true for you DURING THE PAST SEVEN DAYS.

.	Not at all	Rarely	Sometimes	Often
I thought about it when I didn't mean to	.	.	.	.
I avoided letting myself get upset when I thought about it or was reminded of it	.	.	.	.
I tried to remove it from memory	.	.	.	.
I had trouble falling asleep or staying asleep because of pictures or thoughts about it that came into my mind	.	.	.	.
I had waves of strong feelings about it	.	.	.	.
I had dreams about it	.	.	.	.
I stayed away from reminders of it	.	.	.	.
I felt as if it hadn't happened or wasn't real	.	.	.	.
I tried not to talk about it	.	.	.	.
Pictures about it popped into my mind	.	.	.	.
Other things kept making me think about it	.	.	.	.
I was aware that I still had a lot of feelings about it, but I didn't deal with them	.	.	.	.
I tried not to think about it	.	.	.	.
Any reminder brought back feelings about it	.	.	.	.
My feelings about it were kind of numb	.	.	.	.

Scoring:
Not at all = 0; Rarely = 1; Sometimes = 3; Often = 5
Total = total the scores.

Appendix F: Hospital Anxiety and Depression Scale

The statements below are about how you are feeling in yourself.

Please read each statement and **circle the number** next to the answer which comes closest to how you have been feeling in the **past week**. (Please make sure you answer every statement).

a) I feel tense or 'wound up':
- Most of the time....1
- A lot of the time....2
- From time to time, occasionally....3
- Not at all....4

b) I still enjoy the things I used to enjoy:
- Definitely as much....1
- Not quite so much....2
- Only a little....3
- Hardly at all....4

c) I get a sort of frightened feeling as if something awful is going to happen:
- Very definitely and quite badly....1
- Yes, but not too badly....2
- A little, but it doesn't worry me....3
- Not at all....4

d) I can laugh and see the funny side of things:
- As much as I always could....1
- Not quite so much now....2
- Definitely not so much now....3
- Not at all....4

e) Worrying thoughts go through my mind:
- A great deal of the time....1
- A lot of the time....2
- From time to time, but not too often....3
- Only occasionally....4

f) I feel cheerful:
- Not at all....1
- Not often....2
- Sometimes....3
- Most of the time....4

g) I can sit at ease and feel relaxed:
- Definitely....1
- Usually....2
- Not often....3
- Not at all....4

h) I feel as if I am slowed down:
- Nearly all the time....1
- Very often....2
- Sometimes....3
- Not at all....4

i) I get a sort of frightened feeling like butterflies in the stomach:
- Not at all....1
- Occasionally....2
- Quite often....3
- Very often....4

j) I have lost interest in my appearance:
- Definitely....1
- I don't take as much care as I should....2
- I take just as much care....3
- I take more care than I have previously....4

k) I feel restless, as if I have to be on the move:
- Very much indeed....1
- Quite a lot....2
- Not very much....3
- Not at all....4

l) I look forward with enjoyment to things:
- As much as I ever did....1
- Rather less than I used to....2
- Hardly at all....3
- Not at all....4

m) I get sudden feelings of panic:
- Very often indeed....1
- Quite often....2
- Not very often....3
- Not at all....4

n) I can enjoy a good book or radio or TV programme:
- Often....1
- Sometimes....2
- Not often....3
- Very seldom....4

Appendix G: Quality of Life Questionnaire (EQ-5D)

EQ-5D – This is Euro Qual – 5D for completion by the patient. This is a standard questionnaire which is used in large research studies in similar populations.

The next few questions are how you are **at present**. *For each of the five sets of statements below please **circle the number** that **best** describes your own health state **today.***

1. **Mobility**
   I have no problems in walking about 1
   I have some problems in walking about 2
   I am confined to bed 3

2. Self-Care
   I have no problems with self-care 1
   I have some problems washing or dressing myself 2
   I am unable to wash or dress myself 3

3. Usual Activities
   I have no problems with performing my usual activities
   (eg work, study, housework, family or leisure activities) 1
   I have some problems with performing my usual activities 2
   I am unable to perform my usual activities 3

4. **Pain/Discomfort**
   I have no pain or discomfort 1
   I have moderate pain or discomfort 2
   I have extreme pain or discomfort 3

5. **Anxiety/Depression**
   I am not anxious or depressed 1
   I am moderately anxious or depressed 2
   I am extremely anxious or depressed 3

EQ-5D cont.d

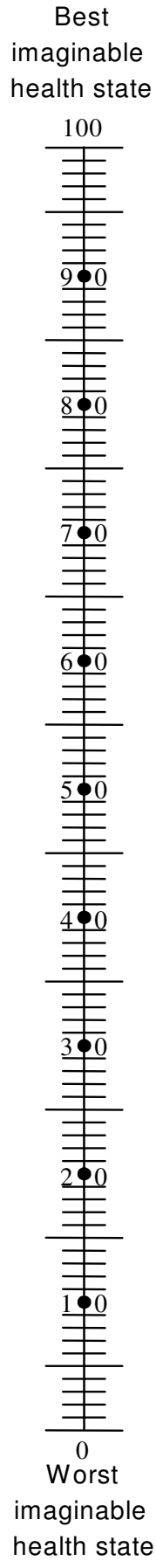
6. Now we would like you to tell us how good or bad is your own health today, in your opinion.

To help you say how good or bad your own health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

Please draw a line from the box below to whichever point on the scale indicates how good or bad you feel your health state is **today.**

Your own health

state today



Appendix H: Summary of changes to Protocol Version 1 (09FEB2005)

Protocol Amendment 1 (21FEB2006)

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6 RESPONSIBILITIES

- Ensure archival of study documentation for a minimum of ~~12~~ *10* years following the end of the study~~, unless local arrangements require a longer period~~

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9 STUDY DESIGN

Table of events

Visit	1 (Baseline)	2	3	
Time	up to -2w	0	+ 2w	+ 3m
Inclusion/exclusion screening	x			
Written informed consent	x			
Randomisation, if applicable	x			
Reason for preference, if applicable	x			
Demography	x			
Medical history	x			
Concomitant medication	x			
Ultrasound	x			
Strength of preference	*x**	~~x*~~	x	
Termination procedure		x		
Adverse events		x	x	x
Concomitant medication		x	x	x
Acceptability			x	x
Satisfaction with care			x	x
Experience of care			x	x
Impact of Event Scale			x	x
Anxiety & Depression Scale			x	x
Quality of Life (EQ-5D)			x	x

moved to fit in with flow of clinics

x* only determined prior to procedure in the preference group

Consent for Qualitative sub-study			x	
Qualitative interview			x	

Alternative methods of collecting the primary and secondary outcome data will be discussed at baseline to ensure maximum follow up:

- The third visit can be performed in a community clinic (based within Sexual & Reproductive Health Services), rather than the hospital setting.
- If participants fail to attend the 2 week follow up visit, contact and data collection will be attempted by telephone~~, followed~~ *or* by postal questionnaire (with an option to complete the questionnaire via the internet)*, according to their consent*. Also if agreeable, a final option of text message will be used to elicit primary outcome data; text messaging may also be used for a visit reminder.
- 3 month follow up data will be collected via postal or web-based questionnaire.

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10.1 INCLUSION CRITERIA

- Women under 16 years of age will be approached where they are determined to be Gillick competent (by the clinical practitioner) and where a parent~~/legal representative~~ is present.

11 SUBJECT RECRUITMENT

For those women less than 16 years of age (minor), a parent ~~or legal representative~~ shall also have the study explained and have opportunity to ask questions. The parent ~~or legal representative~~ will provide written consent at the same time as and in addition to the minor's consent.

Unaccompanied women *of less than 16 years*, or accompanied women with unsuitable representatives, ~~of less than 16 years~~ will not be considered ~~of~~ *for* the study.

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14.1 DATA COLLECTION

Acceptability - This will be determined at 2 weeks and 3 months after the procedure by responses to the closed question 'If you ever have another termination of pregnancy, would you opt for the same method?'. This simple question has been used in previous preference trials of TOP [14, 15] and can, if necessary, be easily determined by phone*, questionnaire* or text message.

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14.2 DATA HANDLING

The quality and retention of study data will be the responsibility of the Newcastle Clinical Trials Unit. All study data will be archived in line with ~~current University~~ *Trust* policy (currently ~~12~~ *10* years).

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16 COMPLIANCE AND WITHDRAWAL

A range of contact processes are also included to maximise capture of primary and secondary data where participants fail to attend the week 2 follow up visit. These include telephone contact (up to ~~2~~ *three* attempts)*,* ~~for all participants to capture the primary variable, and~~ postal questionnaires *(up to two attempts),* or a web-based questionnaire option*, to capture the primary variable*. For agreeable participants text messaging will be used for a visit reminder at week 2 and collection of the primary variable (up to two attempts).

Appendix I: Summary of changes to Protocol Version 2 (03October 2006)

Protocol Amendment 2 (3rdOctober2006)

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The study involves up to 3 hospital visits; the third visit is currently only part of normal care for those patients where it is unclear if medical abortion has been complete or who are experiencing problems. However the RCOG has recently recommended that all women should be offered a follow-up appointment within 2 weeks of abortion [7].

Alternative methods of collecting the primary and secondary outcome data will be discussed at baseline to ensure maximum follow up:

- The third visit can be performed in a community clinic (based within Sexual & Reproductive Health Services), rather than the hospital setting.
- If participants fail to attend the 2 week follow up visit, contact and data collection will be attempted by telephone or by postal questionnaire (with an option to complete the questionnaire via the internet), according to their consent. Also if agreeable, a final option of text message will be used to elicit primary outcome data; text messaging may also be used for a visit reminder.
- 3 month follow up data will be collected via postal or web-based questionnaire.

From month 10 of recruitment, 32 women (8 from each arm) will be invited to join the qualitative sub-study during the 2 week contact. A convenient time will be arranged by the researcher to perform this interview.

Definition of end of study
The end of the study will be the last participant's final study contact, at 3 months follow up.

10 SUBJECT POPULATION

This is a single site study and will be conducted at the RVI in Newcastle upon Tyne; a busy NHS unit which undertakes nearly 1300 terminations a year.

2232 women requesting termination of pregnancy are required for inclusion into the study.

10.1 Inclusion criteria

- Women requesting and accepted for termination of pregnancy at less than 14 weeks' gestation (as determined by ultrasound)
- Women under 16 years of age will be approached where they are determined to be Gillick competent (by the clinical practitioner) and where a parent is present.
- Ability to give written informed consent

10.2 Exclusion criteria

- Pre-existing medical disorder which is an indication for either medical or surgical TOP.

- Non English speaking women (apart from French, Mandarin, Cantonese, Bengali, Urdu & Arabic) due to limited availability of interpreters.
- Previous participation in this trial.
- Current participation in a "drug" related trial.

Sub-study

This sample is neither intended to be statistically representative nor to be a maximum variation sample; sampling will be purposive and sequential. Every woman entering the trial in the period after 10 months recruitment will be invited to join the qualitative sub-study at two week contact. We expect a high rate of refusal to join this sub-study and of attrition amongst those who do. This means that although inclusion and exclusion criteria will be the same as those for the main trial, the sample entering the qualitative sub-study will be highly selected.