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Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639

email: hta@hta.ac.uk
web: www.hta.ac.uk

First trimester progesterone therapy in women with a history of unexplained recurrent miscarriages: A randomised, double-blind, placebo-controlled, multi-centre trial

[The PROMISE (**PRO**gesterone in recurrent **MIS**carriage) Trial]

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Authorised by: Dr Arri Coomarasamy

Signature..... Date.....1/11/2012.....

General Information

This document describes an HTA funded international trial organised by Imperial College London, University of Birmingham and King's College London. The trial will be co-ordinated by the Trial Co-ordinating Centre (TCC) at the University of Birmingham; Clinical Trial Unit (CTU) support is from Maternal Fetal Research Unit (MFRU) at King's College London; and the Principal Centre and the Sponsor is Imperial College London.

The protocol details procedures for entering patients into the trial, as well as conducting and monitoring the research. It is not a guide for management of any specific condition or patient. Amendment may be necessary, and such amendments will be circulated to all Principal Investigators at the participating centres for sharing with the researchers and relevant carers. The most up-to-date version of this document can be found at www.medscinet.net/promise. Any queries should be addressed to Dr Arri Coomarasamy, Trial Manager (a.coomarasamy@bham.ac.uk), at the University of Birmingham, UK.

Version Control

Person authorised to sign the final protocol and amendments: Dr Arri Coomarasamy.

Protocol Versions:

Version 6.2	Change of study end date (dated 1/11/2012)
Version 6.1	Clarification that 'delivery to participant' included 'delivery to participants' home addresses added (dated 15/04/2011)
Version 6.0	Research sites updated (dated 26/11/10)
Version 5.0	Final version accepted by Ethics Committee (dated 28/09/09)
Version 4.0	Version submitted to Ethics Committee (dated 15/07/09)
Version 3	Full protocol submitted to HTA (incorporating MRC and HTA reviewers recommendations)
Version 2	Outline protocol submitted to MRC (which was shortlisted by MRC and handed over to HTA for processing)
Version 1	Document circulated for internal and external peer-review before submission to MRC.

RANDOMISATION: MFRU Clinical Trials Unit, King's College London

www.medscinet.net/promise

Trial Co-ordinating Centre: 0044 (0) 121 623 6835

24-hour Emergency Trial Phone Number : 07711888700

Contents

Study Personnel and Contact Details

	Name and address	Contact number	Email address
Sponsor	Imperial College London Mr Gary Roper, Research Governance Manager Clinical Research Governance Office G02, Sir Alexander Fleming building Exhibition Road, London SW7 2AZ	+44(0)207 594 1188	gary.roper@imperial.ac.uk
Funder	NIHR- HTA (UK) NIHR Coordinating Centre for Health, Alpha House, Enterprise Road, Southampton Science Park, Chilworth S016 7NS	+44(0)238 059 5586	hta@hta.ac.uk
Trial Manager	Dr Arri Coomarasamy Senior Lecturer and Consultant Gynaecologist 3rd Floor, Academic Department Birmingham Womens' Hospital Metchley Park Road, Birmingham B15 2TG	+44(0)771 188 8700	a.coomarasamy@bham.ac.uk
Trial Coordinator	Dr Ewa G Truchanowicz 3rd Floor, Academic Department Birmingham Womens' Hospital Metchley Park Road, Birmingham B15 2TG	+44(0)121 623 6835	e.g.truchanowicz@bham.ac.uk
Chief Investigator	Dr Rajendra Rai Senior Lecturer and Sub-specialist in Reproductive Medicine St Mary's Hospital, Mint Wing South Wharf Road, London W2 1PG	+44(0)207 886 2475	r.rai@imperial.ac.uk
Trial Advisor	Mrs Annette Briley Consultant Midwife Maternal and Fetal Research Unit, Division of Reproduction and Endocrinology, 10th Floor North Wing, St Thomas's Hospital, London SE1 7EH	+44(0)207 188 3641	annette.briley@kcl.ac.uk
Trial Statistician	Mr Paul Seed Senior Lecturer 10th Floor North Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH	+44(0)207 188 3642	paul.seed@kcl.ac.uk
Data Management	Laima Juodvirsiene, Project Manager MedSciNet (TM) UK King's College London, 10th Floor,	+44 (0)20 7188 9853	lj@medscinet.com

	North Wing St Thomas' Hospital Westminster Bridge Road London SE1 7EH		
Health Economist	Formerly Professor Christine Godfrey Current: Mr Steve Parrot Department of Health Sciences, Area 2, Seebohm Rowntree Building, University of York YO10 5DD	+44(0)190 432 1356	cg2@york.ac.uk
Trial Pharmacists	Victoria Latham Clinical Trials Pharmacist St Mary's Hospital Praed Street London W2 1PG	+44(0)2075895111	victoria.latham@imperial.nhs.uk
	Dr. S.Yandouzi University Medical Center Utrecht Pharmacy Heidelberglaan 100, 3584 CX Utrecht The Netherlands Assistant : S. Verboom (s.verboom@umcutrecht.nl)	+31-88-7559902	s.yandouzi@umcutrecht.nl
Principal Investigators	*For St. Mary's Hospital, London* Dr Rajendra Rai St Mary's Hospital, Mint Wing, South Wharf Road, London, W2 1PG	+44(0)207 886 2475	r.rai@imperial.ac.uk
	For Birmingham Women's Hospital Professor Mark Kilby 3rd Floor, Academic Department, Birmingham Womens' Hospital, Metchley Park Road, Birmingham, B15 2TG	+44(0)121 627 2778	m.d.kilby@bham.ac.uk
	For Guy's and St.Thomas' Hospitals Dr Yacoub Khalaf 10th Floor North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH	+44(0)207 188 4138	yacoub.khalaf@gstt.nhs.uk
	For Liverpool Women's Hospital Dr Siobhan Quenby University Department, 1st Floor, Liverpool Women's Hospital, L8 7SS	+44(0) 151 702 4100	squenby@liverpool.ac.uk
	For Sheffield Royal Hallamshire Hospital Professor Tin-Chiu Li Jessop Wing, Tree Root Walk, Sheffield, S10 2SF	+44(0)114 226 1064	tin.li@ath.nhs.uk
	For Southampton University Hospitals Dr Ying Cheong University of Southampton, Level F, Princess Anne Hospital, Coxford Road, Southampton SO16 5YA	+44(0) 2380 796033	y.cheong@soton.ac.uk
	For Ayrshire Maternity Unit Dr Marjory MacLean Crosshouse Hospital, Ayrshire Maternity Unit,	+44(0)156 352 1133	marjory.maclean@aaaht.scot.nhs.uk

	Kilmarnock, KA2 0BE		
	For Academic Medical Center Dr Mariëtte Goddijn Academic Medical Centre, Obstetrics and Gynaecology H4-205, Amsterdam, PO Box 2270 1105 DE	+3120 566 3654	M.Goddijn@amc.uva.nl
	For OLVG Amsterdam Dr Eugenie Kaaijk OLVG Oosterpark 9 1091 AC Amsterdam		E.M.Kaaijk@olvg.nl
	For King's College Hospital Dr Jackie Ross King's College Hospital Early Pregnancy Unit & General Gynaecology Clinic Denmark Hill SE5 9RS	+44 (0) 0203 299 1702	jackie.ross1@nhs.net
	For UMCU Utrecht Drs Yvonne Koot UMC Utrecht Heidelberglaan 100 3584 CX Utrecht		Y.Koot@umcutrecht.nl
	For LUMC (Leiden) Dr Kitty Bloemenkamp LUMC Albinusdreef 2 2333 ZA Leiden		K.W.M.Bloemenkamp@lumc.nl
	For MMC Veldhoven Dr Carolien Koks MMC Veldhoven De Run 4600 5504 DB Veldhoven		c.koks@mmc.nl
	For UMCG Groningen Dr Annemieke Hoek UMCG Hanzeplein 1 9713 GZ Groningen		a.hoek@og.umcg.nl
	For Atrium MC Heerlen Dr Patricia Mercelina MC Heerlen Henri Dunantstaat 5 6419 PC Heerlen		patsxm3@hotmail.com
	For MCLeeuwarden Dr Denise Perquin MCLeeuwarden Henri Dunantweg 2 8934 AD Leeuwarden		Denise.Perquin@ZNB.NL.
	For Isala Klinieken Zwolle Dr Walter Kuchenbecker Isala Klinieken Zwolle		w.k.h.kuchenbecker@isala.nl

	Dokter v Heesweg 2 8025 AB Zwolle		
	For Queen Alexandra Hospital, Portsmouth Dr Nirmala Vaithinlingham Queen Alexandra Hospital Cosham, Portsmouth PO6 3LY	+44(0) 23 9228 6000	nirmala.vaithilingam@porthosp.nhs.uk
	For University Hospitals Coventry & Warwickshire NHS Trust Prof Siobhan Quenby Gynaecology University Hospitals Coventry & Warwickshire NHS Trust Coventry CV2 2DX	+44(0)2476 967405	S.Quenby@warwick.ac.uk
	For West Middlesex University Hospitals Dr Maysoon Backos Women's and Children's Division Twickenham Road Isleworth. Middlesex TW7 6AF	+44 (0)20 8560 2121	maysoon.backos@wmuh.nhs.uk
	For Southern General Hospital Glasgow Dr Judith Roberts The Maternity Unit Southern General Hospital 1345 Govan Road Glasgow G51 4TF	+44(0)141 201 1100	Judith.Roberts@ggc.scot.nhs.uk
	For Royal Devon and Exeter Hospitals NHS Foundation Trust Dr Lisa Joels Wonford Hospital Barrack Road Exeter EX2 5DW	+44(0)1392411611	Lisa.Joels@rdeft.nhs.uk
	For Birmingham City Hospital Dr Ayman Ewies Birmingham City Hospital Dudley Road Birmingham West Midlands B18 7QH	+44(0)121 554 3801	ayman.ewies@nhs.net
	For St Mary's Manchester Dr Edmond Edi-Osagie Saint Mary's Hospital Oxford Road Manchester M13 9WL	+44 (0) 161 276 1234	Edmond.Edi-Osagie@cmft.nhs.uk
	For Luton and Dunstable NHS Foundation Trust Dr Neela Mukhopadhaya Luton and Dunstable NHS Foundation Trust Lewsey Road Luton LU4 0DZ	+44 (0) 845 127 0 127	Neela.Mukhopadhaya@ldh.nhs.uk

	For Nottingham University Hospitals Dr Judith Moore QMC Derby Road Nottingham NG7 2UH	+44 (0) 115 924 9924	Judith.Moore2@nuh.nhs.uk

1. Abbreviations

AE	Adverse Event
AR	Adverse Reaction
APS	Antiphospholipid syndrome
ATC code	Anatomical Therapeutic Chemical Classification Code
BD	Twice daily
BMI	Body Mass Index
BNF	British National Formulary
CAS Number	Chemical Abstract Service Number
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systematic Reviews
CI	Chief Investigator
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRGO	Clinical Research Governance Office (Imperial College London)
CTU	Clinical Trials Unit
CV	Curriculum vitae
DARE	Database of Abstracts of Reviews of Effectiveness
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDU	High Dependency Unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular (injections)
IMP	Investigational medicinal product
IPPV	Intermittent positive-pressure ventilation
ISI	ISI Web of Science Proceedings
ISRCTN	International Standard Randomised Controlled Trial Number
ISO	International Organization for Standardization
ITMS	Integrated Trial Management System
ITU	Intensive Therapy Unit
IVF	In vitro fertilisation
LMWH	Low Molecular Weight Heparin
MA	Marketing Authorization
MFRU	Maternal Fetal Research Unit (at King's College University, London)
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimally Important Difference
MRC	Medical Research Council
mRCT	metaRegister of Controlled Trials database
NICE	National Institute of Clinical Excellence
NIHR-HTA	National Institute for Health Research- Health Technology Assessment
NHS	National Health Service
NHSSTS	NHS Strategic Tracing Services
NNU	Neonatal Unit

OA	Outcome Assessment
ONS	Office of National Statistics
PALS	Patients Advisory and Liaison Service
PSS	Personal Social Services
QA	Quality Assurance
QP	Qualified Person (for release of IMP)
RCOG	Royal College of Obstetricians and Gynaecologists
R&D	NHS Research and Development
REC	Research Ethics Committee
RM	Recurrent Miscarriage
RR	Relative Risk
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCBU	Special Care Baby Unit
SOP	Standard Operating Protocol
SLE	Systemic Lupus Erythematosus
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Co-ordinator
TCC	Trial Co-ordinating Centre
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

3. Synopsis

Title	First trimester progesterone therapy in women with a history of unexplained recurrent miscarriages: A randomised, double-blind, placebo-controlled, multi-centre trial
Acronym	PROMISE
Short title	Progesterone in Recurrent Miscarriages (PROMISE) Study
Objectives	***Principal Objective:*** To test the hypothesis that in women with unexplained recurrent miscarriages, progesterone (400mg pessaries, twice daily), started as soon as possible after a positive pregnancy test (and no later than 6 weeks gestation) and continued to 12 weeks of gestation, compared to placebo, increases live births beyond 24 completed weeks of pregnancy by at least 10%. ***Secondary Objectives:*** 1. To test the hypothesis that progesterone improves various pregnancy and neonatal outcomes (such as reduction in miscarriage rates and improvement in survival at 28 days of neonatal life). 2. To test the hypothesis that progesterone, compared to placebo, does not incur serious adverse effects to the mother or the neonate (such as genital anomalies in the neonate). 3. To explore differential or subgroup effects of progesterone in various prognostic subgroups. (Three subgroup analyses are planned: a)by maternal age (<35, ≥35), b) Number of previous miscarriages (3, ≥4) and c) presence or absence of polycystic ovaries). 4. To perform an economic evaluation for cost-effectiveness.
Trial Design	A randomised, double-blind, placebo-controlled multicentre international study, with health economic evaluation.
Setting	8 hospital outpatient clinics (6 hospitals in England, 1 hospital in Scotland and 1 hospital in Amsterdam, Netherlands).
Number of participants	790 women in total (395 participants in both the progesterone and placebo arms).
Main eligibility criteria	***Inclusion criteria:*** 1. Women with unexplained recurrent miscarriages (3 or more first trimester miscarriages). 2. Age 18 - 39 years at randomisation (likelihood of miscarriages due to chromosomal aberrations is higher in older women; such miscarriages are unlikely to be prevented by progesterone therapy). 3. Spontaneous conception (as confirmed by urinary pregnancy tests). 4. Willing and able to give informed consent. ***Exclusion criteria:*** 1. Inability to conceive spontaneously within 1 year of recruitment. 2. Antiphospholipid syndrome (lupus anticoagulant and/ or anticardiolipin antibodies); other recognised thrombophilic conditions (testing according to usual clinic practice). 3. Uterine cavity abnormalities (as assessed by ultrasound, hysterosonography, hysterosalpingogram or hysteroscopy). 4. Abnormal parental karyotype.

	5. Other identifiable causes of recurrent miscarriages (tests initiated only if clinically indicated): e.g. diabetes, thyroid disease and SLE. 6. Current heparin therapy. 7. Contraindications to progesterone use (e.g. allergy to progesterone).
Study interventions	Progesterone (Utrogestan) pessaries, two capsules of 200mg (400mg), twice daily soon after diagnosis of pregnancy (and no later than 6 weeks gestation) to 12 weeks gestation (or earlier if pregnancy ends before 12 weeks). Placebo pessaries of identical appearance and weight.
Duration of study	4 years 8 months (start date 01/10/2009, end date 01/06/2014)
Randomisation	Participants will be randomised on-line via a secure Internet facility in a 1:1 ratio through a third party independent Integrated Trial Management System (MedSciNet Clinical Trial Framework). A 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables. Stratification variables will be a) number of previous miscarriages (3 or >3), b) age (≤35 or >35 years), c) Polycystic ovaries or not, and d) BMI (≤30 or >30).
Outcome measures	***a) Primary Outcome:*** Live births beyond 24 weeks. ***b) Secondary Outcomes:*** Gestation at delivery; clinical pregnancy at 6 – 8 weeks; on-going pregnancy at 12 weeks (range 11 - 13 weeks), miscarriage rate, survival at 28 days of neonatal life, congenital abnormalities, with specific examination for genital anomalies, and adverse events. ***c) Outcomes for exploratory analyses:*** Antenatal complications (such as pre-eclampsia, fetal growth restriction, preterm rupture of membranes and antepartum haemorrhage); If delivery ≥ 24 weeks, data on mode of delivery, birth weight, arterial and venous cord pH (where available), Apgar scores, and resuscitation; Neonatal outcomes: surfactant use, ventilation support, neonatal complications (such as infection, respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhages and pneumothorax). ***d) Resource use outcomes:*** antenatal, outpatient or emergency visits, inpatient admissions (nights in hospital), maternal admission to High Dependency Units or Intensive Care Units (nights) and neonatal admission to Neonatal Units (nights). ***e) Outcomes for future studies:*** Women will be asked to consent for future evaluation of themselves, their child and the health records of both, and babies will be flagged with the Office of National Statistics (ONS) or equivalent and may be traced through NHSSTS. Although long-term follow up is outside the scope of this trial, we plan to conduct further studies on outcomes such as the composite endpoint of death or neurodevelopmental impairment at two years of age, the Bayley III cognitive scale standardised score at two years of chronological age, and disability classified into domains according to professional consensus. Newborn hospital number and Newborn NHS number for each baby will be recorded to facilitate future follow up studies.

4. Background

4.1 Burden of disease

Miscarriage, the loss of a pregnancy before 12 weeks gestation, is the commonest complication of pregnancy - 1 in 6 clinically recognised pregnancies miscarry.[1] Recurrent miscarriage (RM), the loss of three or more consecutive pregnancies, is a distinct clinical entity. The incidence of RM (1%) is significantly higher than that expected by chance alone (0.4%) and, in contrast to women with sporadic miscarriage, those with RM tend to lose genetically normal pregnancies.[1] Even after comprehensive investigations, a cause for RM is identified in less than 50% of couples.[1] The majority of couples are therefore labelled as having unexplained RM.

Impact on patients and the NHS: RM affects over 6000 couples in the UK every year, and is estimated to cost the NHS £28 million/ year. This estimate includes the costs to the NHS of diagnosis (blood tests and ultrasonography), management of miscarriages (expectant, medical or surgical), investigations for causes of miscarriages (for example, antiphospholipid syndrome, parental karyotype and uterine cavity tests) and hospital bed costs. However, it does not include management of the complications following treatment of miscarriages (such as uterine perforation, infection, bleeding or visceral damage) and any long-term health consequences of miscarriages or miscarriage management (including complications of intrauterine infections and adhesions). Thus the true NHS-perspective costs are likely to be higher than the estimated £28 million/year. The societal costs, including days lost off work and out-of-pocket expenses for patients and partners, can be expected to be far greater.

Recurrent miscarriage also results in substantial adverse psychological impact for the patients; for instance, qualitative studies have shown that the level of distress and the bereavement reaction associated with miscarriages are equivalent to those of women who have suffered the stillbirth of a term baby.[1]

4.2 Current use of progesterone for Recurrent Miscarriage

Current use: We conducted a clinician survey in the UK (n=114, response rate: 102/114=89%), and found that 2% (2/102) clinicians use progesterone routinely and 3% (3/102) use it selectively in pregnant women with a history of recurrent miscarriages. Over 95% (97/102) reported that they do not use progesterone for this indication and the vast majority of these (92/102=90.2%) were willing to recruit to a trial evaluating the role of progesterone treatment for the prevention of recurrent miscarriages.

4.3 Existing Evidence

We have carried out separate systematic reviews to examine (a) effectiveness of progesterone in RM and (b) safety of progesterone in pregnancy.

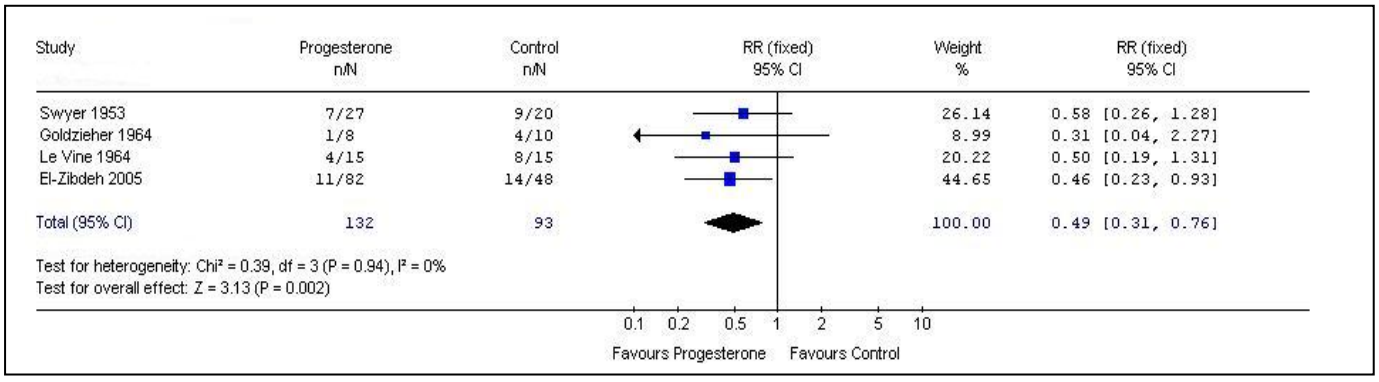
4.3.1 Effectiveness of progesterone in RM:

There are two systematic reviews (1989 [2] and 2003 [3]) that examine the role of progesterone therapy in recurrent miscarriages. However, new evidence[4] has emerged since these reviews were published. Thus we conducted a new systematic review with meta-analysis.
Databases: MEDLINE, EMBASE, CCTR, CDSR, DARE, ISI Proceedings; ISRCTN Register and mRCT database.
Search period: From database inception to January 2008.
Search terms: 'progesterone', 'progestagen', 'progestogen', 'progestin', 'progestational [hormone or agent]', 'progest$'.

Outcomes for the review: 'Miscarriage' [as defined by the primary authors], live birth, gestation at delivery, pregnancy and neonatal outcomes.
Findings: Four randomised trials[4-7] were identified.[†] The quality of the four trials was poor (modified Jadad Quality Scores between 0/5 to 2/5, Table). Participant numbers were small even when the trials were combined in meta-analysis, with only 132 women actively treated with progestagens. However, all four trials showed a trend towards benefit with 42 - 69% decrease in miscarriage rate, but confidence intervals were wide and differences were not statistically significant for all but one of the four trials. Meta-analysis showed a statistically significant reduction in miscarriages (RR= 0.49, 95% CI 0.31 to 0.76, Figure). There was no evidence of statistical heterogeneity in the results (Heterogeneity p-value: 0.94). Data were not available for meta-analysis of the other outcomes.
Interpretation: Although this evidence would be graded level 1a in the evidence hierarchy (as it is a systematic review of randomised trials), our survey of clinicians has shown that it has not resulted in use of progesterone in RM, due to the weak methods and the small sample sizes employed by the four published trials. Nonetheless, the existing evidence presents a powerful reason to proceed with a trial of progesterone in RM.

	Goldzieher 1964 (n=18)	**Le Vine 1964 (n=30)**	**Swyer 1953 (n=47)**	**El-Zibdeh 2005 (n=130)**
Clinical Characteristics				
Population	Analysis restricted to those with a history of 3 or more miscarriages	History of 3 consecutive miscarriages	Analysis restricted to those with a history of 3 or more miscarriages	Unexplained RM (3 consecutive miscarriages, and conditions like APS excluded)
Intervention	medroxyprogesterone 10 mg/day (oral)	hydroxyprogesterone caproate 500 mg/week IM	progesterone pellets 6 x 25 mg inserted into gluteal muscle	Dydrogesterone 10mg BD (oral)
Comparison	Placebo	Placebo	No treatment	No treatment
Duration of treatment	Unclear	Until miscarriage or 36 weeks	Unclear	From diagnosis of pregnancy to 12 weeks
Quality features				
Randomisation method	"sequentially numbered bottles"	Alternation	Alternation	"randomised"; method not given
Allocation concealment	Unclear	Unclear	Inadequate	Unclear
Blinding	Double	Double	No	No
ITT analysis	Unreported	No	Unreported	Yes
Follow-up rates	100%	54% (26/56 excluded)	100%	100%
Jadad Score	2/5	0/5	1/5	0/5

Meta-analysis of the four trials of progestagen use in RM (Outcome: Miscarriage)



[†] There are 14 trials assessing the effects of progesterone in *sporadic* miscarriages (Cochrane review)[3]; these trials should not be confused with trials assessing the effects of progesterone in *recurrent* miscarriages.

4.3.2 *Safety of progesterone supplementation in pregnancy*

There is substantial evidence from IVF practice that progestagen supplementation is safe to the mother and fetus (at the proposed dose for PROMISE Trial of 400mg BD).[8-10] To further explore the question of safety, we conducted a review using the following terms in MEDLINE (1966-2007) and EMBASE (1988-2007): ('progesterone' OR 'progestational agents' OR 'progest$') AND ('adverse effects' OR 'complications' OR 'side effects' OR 'harm') AND 'pregnancy'. A systematic review of observational studies (both cohort and case-control studies) of first trimester sex hormone exposure identified 14 studies, consisting of 65,567 women.[11] The sex hormone in several of these studies was progestagens alone or with other steroids. No harm, particularly any external genital malformation, was found in this review. However, one case-control study has suggested an association between hypospadias and progestagen use.[12] Although findings from a case-control study represent weaker evidence when compared to the better quality evidence from the large cohort studies which do not substantiate this association, all effects of progesterone will be documented in this trial. More specifically, all neonates will be examined for genital abnormalities.

Effects of progesterone on maternal health: Meta-analyses of progesterone use in recurrent miscarriage, in miscarriage,[3] and in the prevention of preterm birth[13] have not shown any evidence of short term safety concerns in the mothers. However, it is not clear whether these trials sought to document maternal side-effects prospectively. In one study, intramuscular 17OHP caused maternal adverse events in 50% of women, largely due to injection site reactions[14] – however, this concern does not apply to our trial, as the route of administration in the PROMISE Trial is vaginal. Side-effects were not reported in recent studies of *vaginal* progesterone in the context of prevention of preterm births[15;16]

4.4 Why is a trial needed?

A trial of progesterone therapy in the treatment of unexplained RM is required as:

1. The existing trials, although small and of poor quality, suggest a large benefit in a condition with substantial morbidity and costs.
2. A recent Guideline by the Royal College of Obstetricians and Gynaecologists[17] and a Cochrane Review[3] have called for a definitive trial to evaluate this research question.
3. Participants in two unpublished surveys (one of women with RM [n=88] and the other of gynaecologists treating women with RM [n=102]) have shown interest in progesterone therapy as well as participating in a potential trial.
4. If proven to be effective, the intervention would represent a low-cost, safe and easily deliverable therapy.

5 Study Objectives

5.1 Primary objective

To test the hypothesis that in women with unexplained recurrent miscarriages, progesterone (400mg pessaries, twice daily), started as soon as possible after a positive pregnancy test (and no later than 6 weeks gestation) and continued to 12 weeks of gestation, compared to placebo, increases live births beyond 24 completed weeks of pregnancy by at least 10%.

5.2 Secondary Objectives

1 To test the hypothesis that progesterone improves various pregnancy and neonatal outcomes (such as reduction in miscarriage rates and improvement in survival at 28 days of neonatal life).
2 To test the hypothesis that progesterone, compared to placebo, does not incur serious adverse effects in the mother or the neonate (such as genital anomalies in the neonate).
3 To explore differential or subgroup effects of progesterone in various prognostic subgroups. (Three subgroup analyses are planned: a) by maternal age (<35 years, ≥35 years), b) Number of previous miscarriages (3, ≥4) and c) presence or absence of polycystic ovaries).
4 To perform an economic evaluation for cost-effectiveness.

6 Participants

6.1 Inclusion criteria

<u>All</u> of the following inclusion criteria must be met to be eligible:

1. Women with unexplained RM (3 or more first trimester miscarriages).
2. Age 18 - 39 years at randomisation (likelihood of miscarriages due to chromosomal aberrations is higher in older women; such miscarriages are unlikely to be prevented by progesterone therapy).
3. Spontaneous conception (as confirmed by urinary pregnancy tests).
4. Willing and able to give informed consent.

6.2 Exclusion criteria

Women cannot be included in this study if <u>any</u> of the following criteria apply:

1. Inability to conceive spontaneously within 1 year of recruitment.
2. Antiphospholipid syndrome (lupus anticoagulant and/ or anticardiolipin antibodies [IgG or IgM]); other recognised thrombophilic conditions (testing according to usual clinic practice).
3. Uterine cavity abnormalities (as assessed by ultrasound, hysterosonography, hysterosalpingogram or hysteroscopy).
4. Abnormal parental karyotype.
5. Other identifiable causes of RM (tests initiated only if clinically indicated): e.g. diabetes, thyroid disease and SLE.
6. Current heparin therapy.
7. Contraindications to progesterone use (e.g. allergy to progesterone). – Please see Section 7.2.

6.3 Withdrawal from study

Following discussion with TMG, a participant can be withdrawn from the trial treatment if, in the opinion of the investigator, it is medically necessary. With premature withdrawal from the study, the study personnel will make every effort to obtain, and record, information about the reasons for discontinuation and any adverse events and to perform all safety assessments.

A patient may voluntarily withdraw participation in this study at any time. If the patient does not return for a scheduled visit, we will try to contact her. We will be aim to document the reason for withdrawal and when possible all safety assessments will be done.

The aim will be to report all data for every patient randomised. All safety data collected from all patients during the study will be analysed with patient's consent. If consent is given, participants who have withdrawn from the study treatment would still be followed up for the remainder of the study for outcome assessment.

Clear distinction will be made as to whether the patient is withdrawing from trial treatments/procedures whilst allowing further follow-up, or whether the patient refuses **any** follow-up. If a patient explicitly withdraws consent to have **any** data recorded their decision will be respected and recorded on the EDC. All communication surrounding the withdrawal will be noted in the patient's records and no further CRFs will be completed for that patient.
Patients can change their minds about withdrawal at any time and re-consent to participate in the trial.

6.4 Informed consent

The consent form was developed after full consultation with patients and representatives. Eligible women will be given verbal and written explanation about the trial, and informed clearly that participation in the trial is entirely voluntary with the option of withdrawing from the trial at any stage, and that participation or non-participation will not affect their usual care. Eligible women can then decide 1) if they wish to participate, 2) if they need more time to consider participation, and 3) if they do not wish to participate; their decision will be respected and adhered to. If the woman needs more time to consider participation, she will be asked to call the trial nurse or researcher when she has decided. If an undecided woman has not called within 14 days, then the trial nurse will contact her. If the initially undecided woman decides to participate later, the trial nurse will arrange a mutually convenient time for the woman to be consented, and will provide the necessary trial information and instructions.

6.5 Service user involvement in research

From the recurrent miscarriage clinics at St Mary's Hospital and Guy's Hospital, London, women with a history of RM were interviewed with a set of structured and unstructured questions to identify their opinions regarding the need for the trial, route of progesterone administration (vaginal, rectal or intramuscular), duration of therapy, suitability of courier transport of trial interventions to the participants, and the choice of outcomes. Five champions were selected from these participants to help us develop Patient Information Sheets and Consent forms, and these documents were reviewed by several other patients with a history of recurrent miscarriages to help us improve the clarity of these document. We have had discussions with the following service user representatives: Ruth Bender-Atik (Director of Miscarriage Association), Liz Campbell (Director of Wellbeing Research) and Officers of RCOG Consumers forum. Ms

Ruth Bender-Atik, Director of Miscarriage Association, will be a member of the Trial Steering Committee.

6.6 Arrangements for persons who might not adequately understand verbal explanations or written information given in English

Where possible, translators will be employed for communicating with potential study participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs. Moreover, we endeavour to provide them with translated information leaflets and written instructions, before they decide on study participation. Such translation of study documents will be done centrally by professional translators, and will be verified by multiple users and interpreters for accuracy and clarity before they are made available to each participating site. Translation via relatives will be avoided. Where translation services are not available, women whose English is not fluent will not be recruited.

6.7 Managing Participant Complaints

Details about complaining is provided in the Patient Information Sheet (Appendix 1). Management of complaints will be according to Imperial College London CRGO SOP: CRO/SOP/013 (available at: http://www3.imperial.ac.uk/pls/portallive/docs/1/45143712.PDF).

7 Interventions

7.1 Progesterone pessaries

Progesterone pessaries 400mg (i.e. two pessaries of Utrogestan 200 mg®) twice daily soon after diagnosis of pregnancy (and no later than 6 weeks of gestation) to 12 completed weeks of gestation (or earlier if pregnancy miscarries before 12 weeks).

Pharmacotherapeutic group ATC code is G03D and the CAS Number is 57-83-0. Utrogestan 200mg Capsules (also marketed as Utrogest, Prometrium, Lugesteron and Progestan in other parts of the world) have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects. Besins Healthcare International hold the Marketing Authorisation (France) for Utrogestan, *including for the indication of luteal phase support to prevent miscarriages* (M07/196).

***7.1.1 Route*:** Immuno-modulatory effect of progesterone at the trophoblastic-decidual interface is the dominant theory on how progesterone may work in women with RM.[1;18] The vaginal route is, therefore, rational since it delivers a greater proportion of drug to the relevant site (the uterus) using the "first uterine pass" effect[19;20]. Furthermore, studies that have used vaginal progesterone in the prevention of preterm birth have shown its effectiveness when given via this route.[13;15;16] The acceptability and availability of interventional drugs are also important considerations which again support the vaginal route of drug delivery. Our discussions with consumer representatives confirm that a vaginal formulation is more acceptable than an intramuscular preparation. These findings are further supported by a recent study in which 12% of participants were unable to tolerate the intramuscular progesterone preparation and declined participation or withdrew from that trial.[14] Of those who did continue, 34% complained of

localised soreness around the injection site. Finally, in our survey of women with RM conducted at St Mary's Hospital (London) and Guy's and St. Thomas' Hospitals (n=88) a very high acceptability of the vaginal route (81/88=92%) was identified. The proposed pessary formulation is also widely available in the UK and worldwide.

7.1.2 Dose. The ideal dose of progesterone for the prevention of RM is unknown. The biologically effective dosage of progesterone pessaries ranges from 200mg once daily to 400mg twice daily according to the Summary of Product Characteristics and the British National Formulary. Progesterone pessaries are commonly used for luteal support in IVF practice.[8] At the usual dosage of 400mg twice daily in IVF practice, no specific concerns on safety have been raised (section 4.3.2). Hence, we consider the dosage of 400mg twice daily of vaginal progesterone as the active treatment to be the optimal choice in order to ensure a clinically effective dose, and minimise the risk of a negative trial result from therapy with a suboptimal dose.

7.1.3 Timing. Treatment will be started as soon as possible after the positive pregnancy test and will continue until 12 weeks gestation. The rationale for stopping progesterone at 12 weeks is that production of progesterone by the corpus luteum becomes secondary to placental production of progesterone after 12 weeks. Furthermore, the only RM trial of progesterone treatment to have reported clearly on duration of treatment demonstrated that the risk of miscarriage was halved when progesterone was given until 12 weeks of gestation (RR 0.46, 95% CI: 0.23, 0.93).[4]

7.2 Contraindications to progesterone use

Women with these conditions are not eligible to take part in the trial (Please see section 6.2 above)

- History of liver tumours
- Severe liver impairment
- Genital or breast cancer
- Severe arterial disease
- Undiagnosed vaginal bleeding
- Acute porphyria.
- History during pregnancy of:
    - idiopathic jaundice,
    - severe pruritus, or
    - pemphigoid gestationis
- The following drugs interact with Utrogestan, and thus women on these drugs are not eligible to take part in the PROMISE trial:
    - Bromocriptine
    - Cyclosporine
    - Rifamycin
    - Ketoconazole

7.3 Placebo pessaries

Placebo pessaries with identical appearance to the progesteraone pessaries will be used in the control arm. The regimen in the placebo arm will be identical to that of the active progesterone arm.

7.4 Concomitant Non-trial treatments

Concomitant therapy will be at the discretion of the care-providing clinicians, and all concomitant treatment and medications will be documented in the EDC. Post-randomisation use of heparin is discouraged unless there is a clear and recognised indication (Note: heparin therapy at the time of randomisation will make a woman ineligible to the trial – Section 6.2).

7.5 Manufacture, Packaging and Labelling of IMP

Active (Utrogestan vaginal 200 mg®) and placebo pessaries will be manufactured and packaged (assembled) by Besins Healthcare International[†] to Good Manufacturing Practice Standards (GMP; EU Directive 2003/94/EC) and in compliance with Good Clinical Practice (GCP; Clinical Trials Directive 2001/20/EC) requirements, and released by a Qualified Person. Besins Healthcare International have the necessary Manufacturing Authorisation for both Utrogestan and placebo pessaries.

Packaging of IMP will be carried out by Besins Healthcare International. The drug package ("patient pack carton") will contain the entire supply required for the 8 week treatment period. As the treatment regimen is two Utrogestan 200 mg® or placebo pessaries, twice daily, for 8 weeks, the drug package for each participant will contain 224 pessaries (2 [pessaries] x 2 [twice daily] x 7 [seven days per week] x 8 [for eight weeks] = 224). The total number of pessaries purchased will include a 5% overage to allow for damages and QA samples

Labelling of the drug packages is in compliance with Part 2 of Schedule 3 to the UK Medicines for Human Use (Clinical Trials) Regulations 2004, ensuring protection of the subject, traceability and proper identification of the product and trial. A sample label is given in appendix 5.

7.6 Storage, dispensing and Return

The study drugs will be stored and dispensed from two study pharmacies (St.Mary's Hospital, London and Academic Medical College, Amsterdam):

Victoria Latham
Clinical Trials Pharmacist
St Mary's Hospital
Praed Street London W2 1PG
+44 2075895111
victoria.latham@imperial.nhs.uk
Dr. S.Yandouzi
University Medical Center Utrecht
Pharmacy
Heidelberglaan 100,
3584 CX Utrecht
The Netherlands
assistant : S. Verboom (s.verboom@umcutrecht.nl) telnr +31-88-7559902
s.yandouzi@umcutrecht.nl

[†] Laboratoires BESINS INTERNATIONAL
3, rue du Bourg l'Abbé
75003, Paris, France

All pharmacies will comply with the relevant guidelines and regulations (including, in the UK, the Duthie report of 1988 and the Royal Pharmaceutical Society Practice Guidance on Pharmacy Services for Clinical Trials, 2005) as well as the Imperial College London CRGO SOP CRO/SOP/026 (available at: http://www3.imperial.ac.uk/pls/portallive/docs/1/45143715.PDF).

Trial drugs will be stored separately from normal pharmacy stock in an area with restricted access. Drugs that are returned by patients or have expired will be stored separately from unused trial medicines. Clinical trial medication will be dispensed against an appropriate prescription form that carries the title the PROMISE Trial, the Eudract number 2009-011208-42, patient's name, date of birth and identification number, and a unique code number (as provided by the Trial Management Framework at the randomisation step).

Detailed dispensing records will be kept by each dispensing pharmacy including participant study number and name, code number, batch number, expiry date, dose and date of dispensing.

All unused study drug, including undispensed supplies and supplies returned by patients will be retained until the end of the study. St Mary's Hospital Pharmacy in the UK (and University Medical Center Utrecht Pharmacy in the Netherlands) will be involved in the reconciliation of medicines returned by trial patients and the disposal of unused medication, in compliance with the guidance from Regional Quality Assurance pharmacists' document on Waste Disposal.

7.7 Known side-effects

Known side effects of progesterone include:

- premenstrual-like syndrome (including bloating, fluid retention, breast tenderness)
- weight change
- nausea
- headache
- dizziness
- insomnia
- drowsiness
- depression
- change in libido
- skin reactions (including urticaria, pruritus, rash, acne)
- diarrhoea and flatulence
- jaundice
- pyrexia
- acne or rash
- alopecia

7.8 Dose Modification for toxicity

For non-serious side-effects, the dosage can be reduced to 200mg twice daily (one pessary in the morning and one at bedtime) at the discretion of the care-providing clinician, without unblinding treatment allocation. Dose modification should be noted on the CRF with gestation and date on which such change was implemented. For serious adverse event handling, please see section 12.

7.9 Overdose

Symptoms of overdose of progesterone may include somnolence, dizziness and euphoria. Treatment is observation and symptomatic and supportive measures should be provided, as required.

7.10 Compliance assessment

Our experience with research in RM women is that they are highly motivated and generally have high compliance with therapy advice. However, we will evaluate compliance by "pill-counting". Prepaid envelopes will also be given by the local research nurses to enable women to return completed, partially used and unused blister packages each month to the trial centres. The research nurse will receive the empty/partially used/unused blister packs at the local centres, and will document this in the database for each trial participant. This will be reviewed monthly by the Trial Management Team. In an effort to improve compliance, women who fail to return the blister packs from the previous 4 weeks, whether empty or not, using the freepost envelope, will be contacted by telephone or email by the research nurse for advice and support. The unused medicine will be sent to St Mary's Hospital Pharmacy for destruction and disposal.

Non-compliance is defined as less than 80% usage of trial medicines. Non-compliant patients will be interviewed (face-to-face or via telephone) in an attempt to establish the reason(s) for non-compliance.

8 Study outcomes

8.1 Primary outcome:

Primary outcome is live birth beyond 24 weeks of gestation.

8.2 Secondary outcomes:

- clinical pregnancy at 6 – 8 weeks;
- on-going pregnancy at 12 weeks (range 11 - 13 weeks),
- miscarriage rate,
- gestation at delivery
- survival at 28 days of neonatal life, and
- congenital abnormalities, with specific examination for genital anomalies

8.3 Exploratory outcomes

Outcomes for exploratory analyses include:

- Antenatal complications (such as obstetric cholestasis, pre-eclampsia, fetal growth restriction, preterm rupture of membranes and antepartum haemorrhage);
- If delivery ≥ 24 weeks, data on mode of delivery, birth weight, arterial and venous cord pH, Apgar scores, and resuscitation;
- Neonatal outcomes: surfactant use, ventilation support (days on IPPV, CPAP and oxygen; discharge on oxygen), neonatal complications (such as infection, respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhages and pneumothorax).

8.4 Resource use outcomes:
Antenatal, outpatient or emergency visits, inpatient admissions (nights in hospital), maternal admission to HDU or ITU (nights) and neonatal admission to SCBU or NNU (nights).

8.5 Outcomes for future studies
Women will be asked to consent for future evaluation of themselves, their child and the health records of both, and babies will be flagged with the Office of National Statistics (ONS) or equivalent. Although long-term follow up is outside the scope of this trial, we plan to conduct further studies on outcomes such as the composite endpoint of death or neurodevelopmental impairment at two years of age, the Bayley III cognitive scale standardised score at two years of chronological age, and disability classified into domains according to professional consensus. Hospital number and NHS number for each baby will be recorded to facilitate future follow up studies.

9 Study Design

9.1 Design
A randomised, double-blind, placebo-controlled multicentre study, with health economic evaluation.

9.2 Setting
Recurrent miscarriage clinics in the participating centres.

9.3 Randomisation and treatment allocation
Participants will be randomised online via a secure Internet facility in a 1:1 ratio through a third party independent Integrated Trial Management System (ITMS MedSciNet Clinical Trial Framework) that has been designed, developed and delivered according to ISO 9001:2000 standards, and compliant with FDA CFR21:11 requirements (Appendix 7).

A 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables. Stratification variables will be a) number of previous miscarriages (3 or >3), b) age (≤35 or >35 years), c) Polycystic ovaries or not, and d) BMI (≤30 or >30).

If the eligibility criteria are met, the Integrated Trial Management System (ITMS) will perform minimisation randomisation, and generate the "code number" which is linked to the medicinal product held by the trial pharmacies.

The ITMS will also be utilised to capture baseline and outcome data, for contemporaneous data-cleaning, to produce reports for DMC, and maintain an audit trail.

9.4 Participant flow through the trial
The anticipated participant flow through the trial is provided in the flowchart below. This flowchart has been developed following discussions amongst the researchers, clinicians, recurrent miscarriage patients and representatives of the patient groups.

9.4.1 Approaching potential participants

Potential participants are identified from 1) dedicated recurrent miscarriage (RM) clinics, or 2) other hospital clinics in which the caseload includes a substantial number of women with RM. Potential participants will be identified by clinic doctors, nurses, and study-specific local research nurses, after having received appropriate training relating to the trial.

The clinic doctor, nurse or study-specific research nurse will approach eligible women. The potential participants will be informed about the study. They will be clearly advised that participation in the study is entirely voluntary with the option of withdrawing from the study at any stage, and that participation or non-participation will not affect their usual care. Potential participants will be provided with the Patient Information Sheet (Appendix 1) and given time to consider their involvement.

Eligible women who have been approached for participation in the study will have as much time as they require to decide whether they wish to take part and consent for the study, provided this is *before they become pregnant*.

9.4.2 Recruitment

If a woman agrees to participate in the trial, written consent (Appendix 2) is obtained by the clinician or research nurse. Baseline data and medical data are collected, anonymised and stored in the electronic Integrated Trial Management System (ITMS, Appendix 7). Any identifying information is collected and stored in a password-protected local database on a secure limited access computer (Appendix 4).

The investigator and the participant will both sign the consent form, and the original will be kept in the Investigator Site File, one copy given to the participant and a copy will be retained in the participant's hospital records.

9.4.3 Pregnancy and delivery of trial drug

The woman is given instructions to notify the research nurse by telephone as soon as she conceives (a positive urinary pregnancy test). It is expected that she will be about 4 weeks pregnant (4 weeks from last menstrual period) at this stage. When the research nurse receives the call from the woman, she will obtain details about this pregnancy and recheck the woman's history to ensure she is still eligible for the trial. If the woman remains eligible, the nurse will randomise her to one of the two trial interventions on the ITMS (section 9.3). The research nurse will arrange the trial pharmacy to dispatch the trial intervention pack (either progesterone or placebo) to the local participating centre or the participant's home address within 72 hours of the telephone call. The research nurse will then provide the woman with instructions. In cases where the delivery is directly to the participant the research nurse will contact the participant to ensure that they received the treatment pack and they fully understand how to use the supplied pessaries. This communication will also offer the opportunity to answer any questions the participant may have. The woman is expected to start the trial intervention on the day it is received, and continue until 12 completed weeks of gestation. The research nurse will call the woman 3-4 days after the trial medicine is provided. The purpose of this call would be to ensure a) the participant has started taking the medicine, and b) address any queries. In the event of the pessaries being mislaid, the woman will be instructed to call the research nurse who will liaise with the Trial Management Group to arrange a further supply of the same type of intervention.

9.4.4 Outcome assessments:

1 The research nurse will call the participant between 6-7 weeks of gestation to ensure she has an ultrasound appointment by her usual carers, before 8 weeks of gestation. If one has not

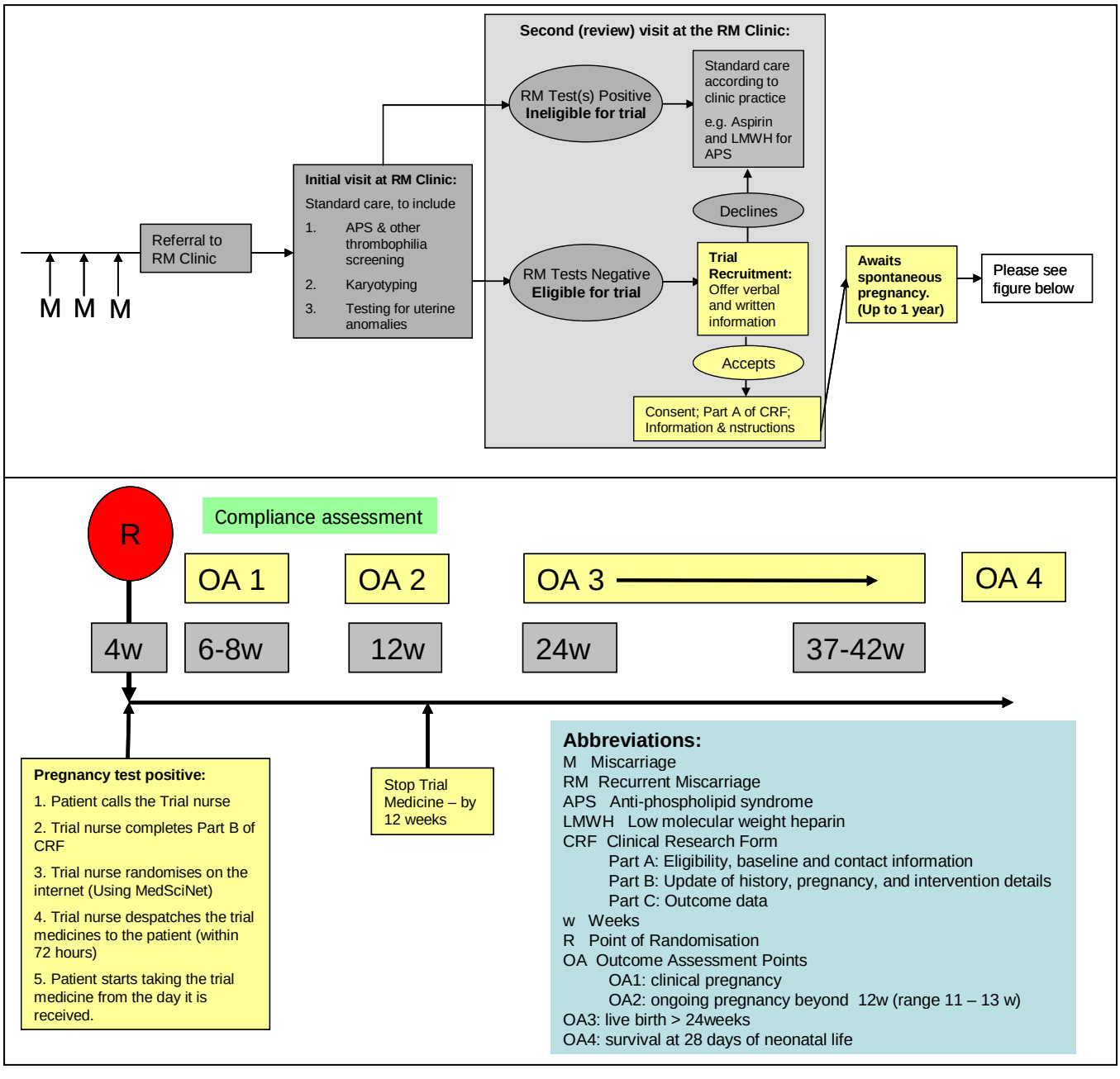
been booked, then the nurse will assist with booking. The research nurse will phone the woman back within 3-5 days of the scheduled date for ultrasound to obtain the findings.

2 The research nurse will call the participant between 10-12 weeks of gestation to ensure she has an ultrasound appointment by her usual carers for 12-14 weeks of gestation. If one has not been booked, then the nurse will assist with booking. The research nurse will phone the woman back within 3-5 days of the scheduled date for ultrasound to obtain the findings. The nurse will record the expected date of delivery (EDD) at this stage.

3 The third outcome assessment is conducted after delivery to gather data on various outcomes. The research nurse will call the participant two weeks after the EDD to obtain the final outcome. Prompts on the Integrated Trial Management System will alert the research nurse when each trial participant reaches her due delivery date. The local research nurse will also check birth registers and in-patient records to track hospital admissions and pregnancy outcomes.

4 The fourth and final outcome assessment is conducted after 28 days of delivery to gather data on various outcomes.

Women in the trial will continue to be managed by their clinical teams throughout their pregnancies, according to local protocols. Each participant will also be given a freepost postcard to complete and return to the trial centre following her baby's birth, thus notifying the research team when she has delivered.



10 Statistical considerations

10.1 Proposed sample size

We plan to randomise 790 women in total (395 participants each in the progesterone and placebo arms). To detect a Minimally Important Difference (MID) of 10% in live birth beyond 24 weeks (from 60% to 70%, odds ratio 1.56), for an alpha error rate of 5% and beta error rate of 20% (i.e. 80% power), 376 women will need to be randomised to the intervention arm, and 376 women to the control arm (752 in total). However, assuming and adjusting for a worst case scenario of a loss to follow-up rate of 5%, the total number of participants required will be 790 (395 in each arm of the trial).

The Minimally Important Difference of 10% was defined following consultations amongst health care practitioners, patients and representatives of patient bodies. However, it should be noted this difference is much smaller than what should be expected from the existing literature (section 4.3.1), which has shown that the risk of miscarriage is halved with progesterone therapy (RR 0.49, 95% CI: 0.31, 0.76). Hence, assuming a conservative actual absolute difference of 15% in live births beyond 24 weeks, 790 participants (after accounting for 5% attrition) will provide a power of 99%.

The 60% baseline (control) event rate is derived from a comprehensive audit carried out at the largest RM unit in the UK (St Mary's, London) covering the period from 1998 - 2005 that showed the chances of live birth are 61.8% (698/1129) after 3 miscarriages, 60.3% (350/580) after 4 miscarriages, 47.6% (109/229) after 5 miscarriages and 42.3% (82/194) after ≥ 6 miscarriages. However, as there is previously published evidence[21] to suggest a higher control event rate, we have performed a sensitivity analysis on the power calculations in which we have assumed a higher control event rate of 70%. For a 10% absolute difference in live birth beyond 24 weeks, and for an alpha error rate of 5%, 790 participants (after accounting for 5% attrition) will give a power of 89% (a higher figure than the 80% power when the control event rate is estimated to be 60%). We believe it is prudent to work on the assumption of a lower control event rate for power calculation as this in fact represents a worse case scenario and the sample size requirements on the lower event rate provide sufficient (and in fact higher) power for a higher control event rate. All power calculations noted above use two-sided binominal testing.

10.2 Planned statistical analysis

The Trial Steering Committee will approve the data analysis plan and will also approve any amendments. Any deviations from the original plan will be documented and justified in the final report. The trial statistician will analyse the results based on treatment code. Only after the analysis is complete will the actual treatment arms corresponding to the treatment codes will be revealed.

The analysis will be by intention-to-treat. Every attempt will be made to gather data on all subjects randomised, irrespective of compliance with the treatment protocol. If there are a substantial number of protocol violations, a separate per-protocol (secondary) analysis will be conducted. The principles of analysis are as follows:

Step 1: Summarising trial data. Baseline data and outcome data will be separately summarised. For continuous variables, we will examine the distribution of the observations, and if normally distributed then we will summarise them as means with standard deviations. If they are not normally distributed, then medians and inter-quartile ranges will be reported; additionally, geometric means and standard deviations will be used for data where distributions appear to be log-normal. For categorical data, we will provide proportions (or percentages). In addition to

the baseline and outcome data, we will also summarise the recruitment numbers, those lost to follow-up, protocol violations and other relevant data. The flow of patients through the trial will be summarised using a Consort diagram.
Step 2: Inter-group comparisons. For binary outcomes, results will be expressed as a Risk Ratios (RR) with 95% confidence intervals. For continuous outcomes, treatment effects will be summarised as mean differences or ratios as appropriate. For economic data, bootstrapped confidence intervals will be used for the difference in the arithmetic mean. Although p-values will be reported for the main outcomes, the focus will be on providing 95% confidence intervals around point estimates as these are more useful in interpreting the findings of the trial.
Step 3: Sub-group analysis. Three subgroup analyses are planned: a) Maternal age: (<35, ≥35), b) Number of previous miscarriages (3, ≥4) and c) presence or absence of polycystic ovaries. In each case, an interaction test will first be used to determine whether there is a basis for treating the groups separately. In addition, post-hoc subgroup analysis will be used for the purpose of hypothesis generation.
Step 4: Adjustments and sensitivity analyses. If randomisation fails to achieve balanced groups, linear or logistic regression will be used to adjust for the imbalance. We will adjust for missing data using multiple imputations. Where differences arise, we will give greater weighting to the primary analysis in Step 2 rather than step 4 in the interpretation of trial findings.

10.3 Interim analyses and Stopping rules

Interim analyses of principal safety and effectiveness endpoints will be conducted on behalf of an independent DMC (Data Monitoring Committee). These will be considered together with a report of the Serious Adverse Events. The trial statistician will be unblinded to the level of groups "A" and "B". The meaning of "A" and "B" will be made known to the DMC separately, if appropriate. The first interim analyses will be undertaken after the primary outcome data are available for the first 100 participants, and thereafter at annual intervals. Effectiveness and futility criteria will be defined by the Data Monitoring and Ethics Committee (DMC). The charter for the DMC will include a specific remit for reviewing emerging data from other trials using progesterone in RM patients.

The following may result in the trial being terminated:

- Interim analysis showing overwhelming evidence of effectiveness/ ineffectiveness, with a nominal interim alpha likely to be set at 0.001 using O'Brien and Fleming alpha spending rules.
- Major safety concerns.
- Insurmountable issues with trial conduct.
- A change in opinion of the REC.
- A regulatory decision or sponsor withdrawal.

Recruitment at a particular study site may be stopped for reasons of low recruitment or compliance issues. The sponsor reserves the right to discontinue this trial at any time for safety, overwhelming evidence of effectiveness or ineffectiveness or any other reasonable reasons, however, only after taking advice from the Trial Steering Committee and Data Monitoring Committee.

11 Health Economics

An economic evaluation will be integrated into the trial design. Data will be collected on the health service resources used in the treatment of each woman and infant during the period between randomisation and hospital discharge. Data will be captured electronically on the duration and intensity of antenatal, intrapartum, postnatal and neonatal care, based on standard criteria for level of care, as well as maternal and neonatal complications. Wider health care utilisation will be quantified using a service use questionnaire. For standard maternal and neonatal care, UK unit costs will be applied from national sources. The unit costs of rarer events and complications will be derived from the participating centres financial accounts allowing for apportionment of management and capital costs to determine long run marginal opportunity costs equivalent to other national sources. Where possible such data will be based on the average costs of the participating centres adjusting for any national differences, e.g. London weighting. These costs data will be combined with outcome data, in the form of a cost effectiveness analysis.

The primary cost-effectiveness output would be the cost per additional birth over 24 weeks' gestation. The analysis will take a NHS and PSS (Personal Social Services) perspective and follow NICE guidance for health care evaluations (NICE, 2008).

A systematic search will be made of models of the longer term consequences for infants in terms of quality of life and health care costs to model the fuller longer term outcomes of the two arms of the trial. Using modelling techniques a cost-utility analysis will be performed, again taking a NHS and PSS perspective. Results will be presented using cost-effectiveness acceptability curves (Fenwick, 2001).

References

Fenwick, E., Claxton, K. and Sculpher, M. (2001) Representing uncertainty: the role of cost-effectiveness acceptability curves, Health Economics, 10, pp779-787

National Institute for Health and Clinical Excellence (2008) Guide to the methods of technology appraisal. LONDON: NICE

12 Adverse events

The PROMISE pharmacovigilance procedures, including adverse event gathering, documentation, validation, evaluation and reporting, are based on the following four sources of good practice:

1. MRC/DH joint project, Work stream 6 on Pharmacovigilance (Jan 2007)
2. ENTR/CT3 Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (April 2006)
3. The EU Clinical Trials Directive (2001/20/EC)
4. Imperial College London SOP on Recording, Managing and Reporting Adverse Events in the UK: CRO/SOP/001
   (URL: http://www3.imperial.ac.uk/pls/portallive/docs/1/45143701.PDF)

We will proactively seek evidence of adverse events. Each participant will be asked at each trial visit or interview about hospitalisations, consultations with other medical practitioners, disability or incapacity or any other adverse events.

12.1 Definitions

The table below summarises the standard definitions that would be followed:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
Adverse Reaction (AR)	Any untoward and unintended responses to an investigational medicinal product related to any dose administered Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey, in general, that there is evidence or argument to suggest a causal relationship.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information. Comment: When the outcome of the adverse reaction is not consistent with the applicable product information, this adverse reaction should be considered as unexpected.
Definition of Seriousness: Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any AE, AR or UAR that at any dose: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect Comment: Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/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. *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. The definition of seriousness above reflects the definition used in the EU Directive, and from EudraCT guidance.

The table below provides guidance on causality assessment:

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship

* If the adverse event is serious and unexpected, the possible, probable and definitely related will be notified to the MHRA, the REC and the Imperial College London Research Governance Office as SUSARS.

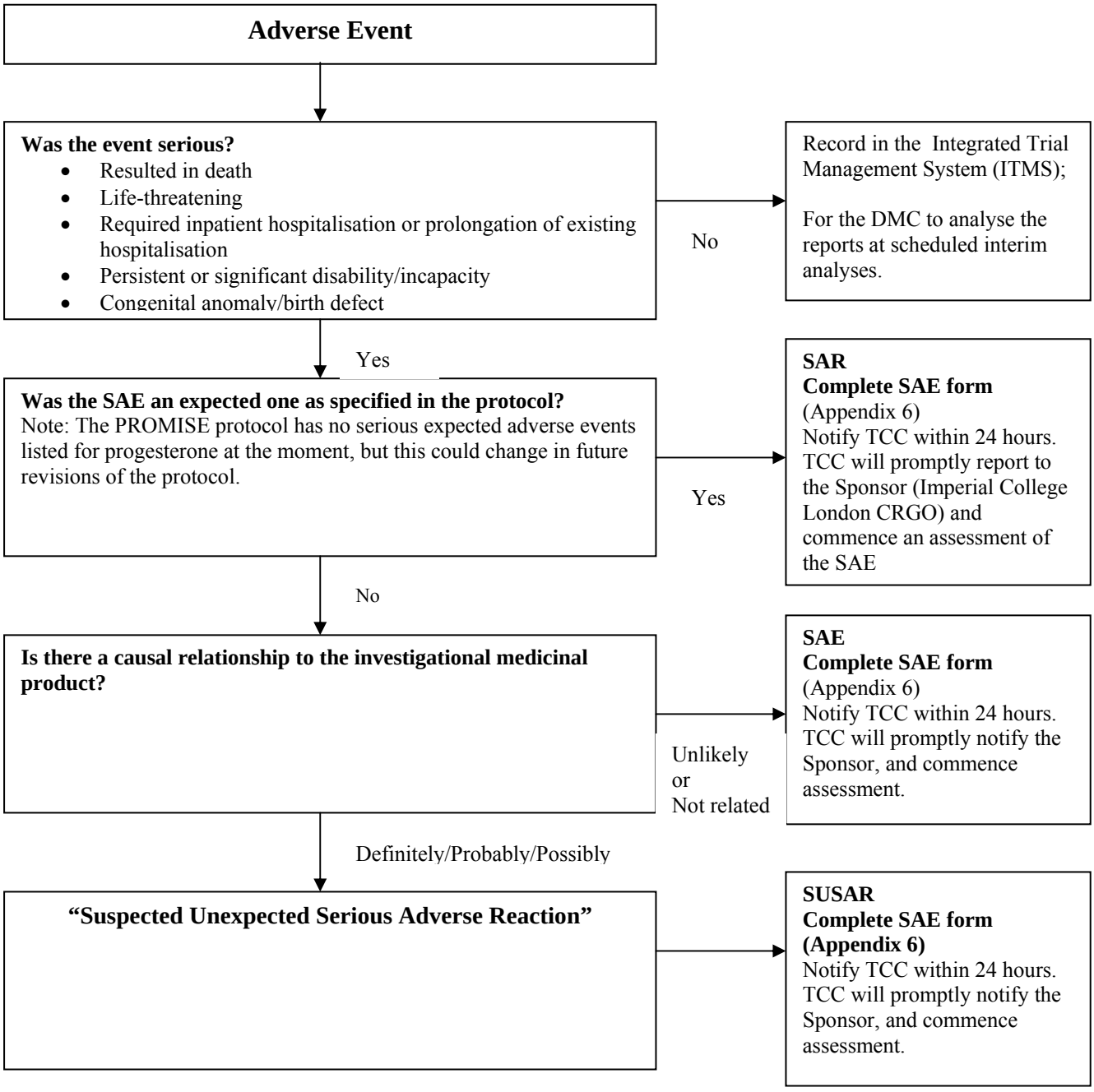
12.2 Reporting of adverse events

The flowchart below details the process for assessing and notifying adverse events. The 'causality', 'expectedness', and 'seriousness' of an adverse event will primarily be assessed by the Trial Co-ordinating Centre (TCC), although local investigators and the Sponsor (Imperial College London Clinical Research Governance Office) may also carry out these assessments. If there is a difference in the assessments, then the "worst case" assessment will be used for reporting.

The investigators will notify adverse events to the TCC which will then inform the Sponsor (Imperial College London). The Sponsor will report to the MHRA and the Main Ethics Committee, or the equivalent bodies in Netherlands, as appropriate.

Six-monthly and annual safety reports and safety line listings will be reported to standard formats (*ENTR/CT3 Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006*).

Adverse events assessment and notification to the Trial Co-ordinating Centre (TCC).



Contact details for reporting SAEs and SUSARs
Fax: 0044(0)121 6266619, Urgent Attention of Dr A Coomarasamy, PROMISE TCC
Email attachments of SAE forms to: a.coomarasamy@bham.ac.uk
Tel: 0044(0)121 623 6835 (Mon to Fri 09.00 – 17.00)

12.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The form for reporting SUSARs is given in Appendix 6, and assessment and reporting processes are given in the flowchart on the previous page.

Regardless of treatment allocation, we will assess seriousness, causality and expectedness as though the patient was on the active drug (progesterone). Cases that are considered serious, unexpected and possibly, probably or definitely related (i.e. possible SUSARs) will be unblinded, as appropriate. A SUSAR which is fatal or life-threatening will be reported as soon as possible and in any event within seven days. A SUSAR which is not fatal or life-threatening will be reported as soon as possible and in any event within 15 days of the event.

The investigators responsible for the conduct of a trial will be kept informed of any SUSARs that occur.

12.4 Procedures for breaking randomisation codes

Breaking the code should only be done in the event of a medical emergency in which the treatment of the emergency requires the knowledge of the actual drug received. In the event that an investigator or the care-providing clinician requires that the treatment allocation is revealed, the Integrated Trial Management System would allow the Trial Manager (Dr A Coomarasamy or a designee) or the Clinical Trial Pharmacy to break the code. Any requests to break the code should therefore be directed to the Trial Co-ordinating Centre (between 9am to 4pm, weekdays) or directly to the Trial Manager or designee who will be accessible via a 24 hour trial mobile phone (Tel: 07711888700). The investigator or care-providing clinician will be asked to provide the date, name of person requesting the blind to be broken, a reason why and any other relevant information.

13 Trial Management and Monitoring

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social Care, 2005.

13.1 Trial start-up and protocol amendments

The trial will not be initiated before the trial has received approval from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Moreover, before the study can start, the PROMISE protocol will need to be signed off by the chairs of TSC and DMC, and the Trial Master File will need to be deposited in the TCC, and all the contact mechanisms (particularly telephones for the TCC and Trial Manager) activated. Should a protocol amendment be made that requires MHRA and/or REC approval, the changes in the protocol will not be instituted until the amendment, revised consent form and participant

and GP information sheets have been reviewed and received approval/favourable opinion from the MHRA and REC. A protocol amendment intended to eliminate an apparent immediate hazard to participants will be implemented immediately and the MHRA, R&D and REC will be notified as soon as possible and an approval will be requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately and the REC will be informed.

The person authorised to sign any amended protocol is Dr A Coomarasamy, PROMISE Trial Co-ordinating Centre, 3rd Floor, Birmingham Women's Hospital, Metchley Park Road, Edgbaston, Birmingham, B15 2TG. To obtain the most recent version of the protocol contact TCC at a.coomarasamy@bham.ac.uk or log on to www.medscinet.net/promise. Revised protocols will be identified by version number and date.

13.2 Trial Management

The trial will be managed from a central Trial Co-ordinating Centre (TCC). TCC is a secure office in the Academic Department of the University of Birmingham (UoB), and will be manned by the Trial Manager, Trial Co-ordinator and a research nurse, with support from trial statistician, data manager, health economists and trial advisors. The day-to-day co-ordination of the trial will be the responsibility of the Trial Manager (TM) and the Trial Co-ordinator (TC). The TM and TC will report to the Trial Management Group (TMG), which in turn will report to the Trial Steering Committee (TSC) [Please see figure in Section 13.4 below]. There will be documented managerial lines of responsibility and reporting; specifically the recruitment nurses will be responsible for accurate data collection and data entry. They will be accountable to the trial coordinator, who in turn will be accountable Trial Manager, and Trial Manager to TMG.

13.3 Trial Monitoring

Please see section 10.3 on Interim analysis and section 13.4.3 on DMC.

Trial will be monitored according to the Imperial College London standard operating protocols: CRO/SOP/015 (http://www3.imperial.ac.uk/pls/portallive/docs/1/45143709.PDF) and CRO/SOP/018 (http://www3.imperial.ac.uk/pls/portallive/docs/1/45143710.PDF).

The purpose of monitoring will be to protect the rights and well-being of trial participants, ensure the reported trial data are accurate, complete, and verifiable from source documents, and the trial is compliant with GCP and other regulatory and good practice guidance. Participating centres will be continuously monitored by the TCC by checking incoming electronic forms for compliance with the protocol, consistency of data, missing data and timing. TCC staff will be in regular contact with centre personnel by phone or email to check on progress and deal with any queries they may have. In addition, periodic site monitoring may be conducted by the TCC or the Sponsor (Imperial College London) to cover issues such as:

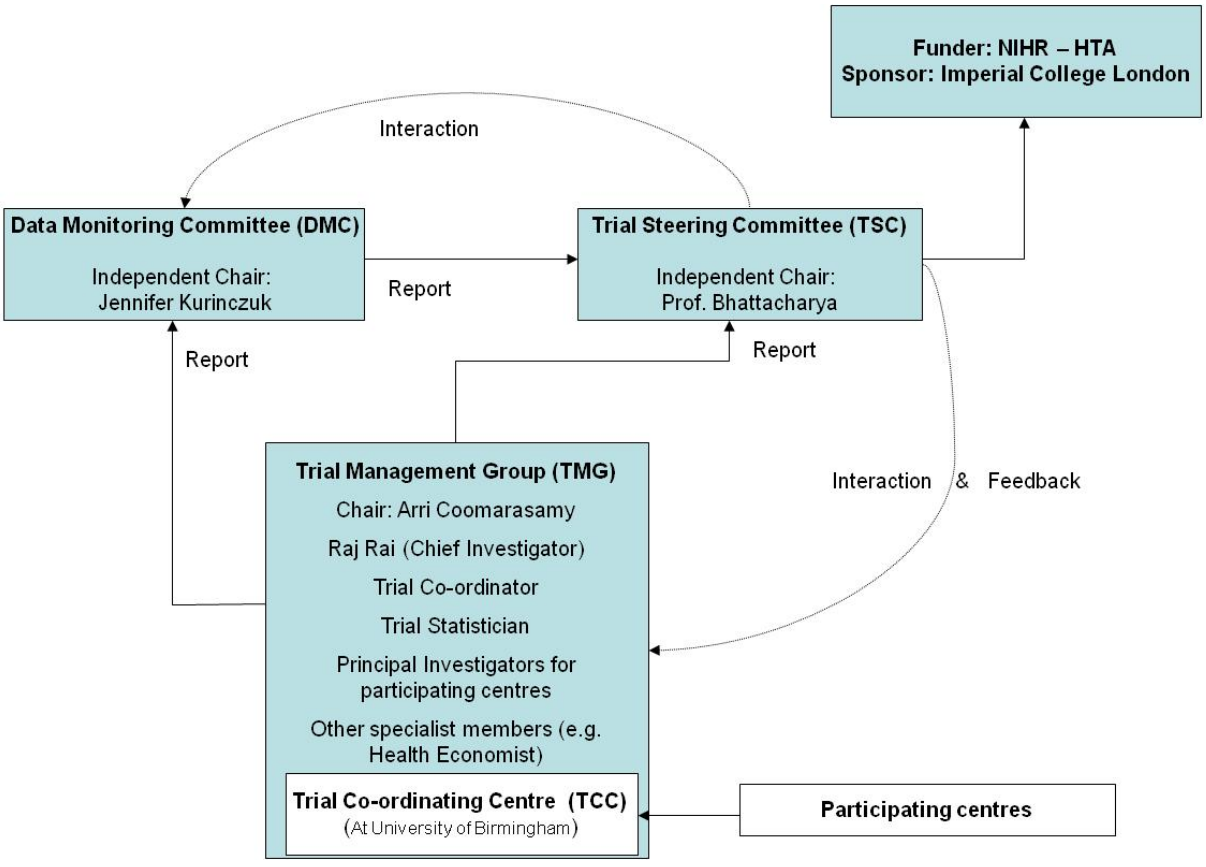
- Reviewing understanding of the protocol and trial procedures by the trial staff.
- Verifying that the staff at the site have access to the necessary documents.
- Verifying selected data items and/or serious adverse events recorded compared with data in the clinical records to identify errors of omission as well as inaccuracies.
- Verifying the existence of participants against clinic records and other sources.

On site monitoring will be carried out as required. Investigator meetings will be held at least annually for learning, updating and sharing. Monitoring visits will be followed by a monitoring report, summarising the findings during the visit and recommending remedial actions as necessary.

An audit of the Trial Master File will be conducted by the Trial Manager or designee at least annually and an audit report will be made available to the Trial Steering Committee. All meetings will be minuted.

13.4 Trial Oversight Bodies

Relationship between the three Trial Oversight bodies (TMG – Trial Management Group, TSC – Trial Steering Committee, and DMC – Data Monitoring Committee) is illustrated in the figure below:



13.4.1 Trial Management Group

The TMG will direct and oversee the running of the trial from the Trial Co-ordinating Centre (TCC). The Trial Management Group (TMG) is comprised of the Trial manager (Dr Arri Coomarasamy, Chair), Chief Investigator (Raj Rai), Trial Co-ordinator, Principal Investigators from each participating centre, trial statistician, health economist and data manger. The TMG

will report to TSC (or directly to DMC if necessary) any issues relating to the monitoring and auditing of the research.
TMG will meet face-to-face or via teleconference, and the action points will be implemented via the TCC. Trial Management Group (TMG) will meet weekly in the early stages of the trial, and regularly as required thereafter, but at least monthly. In addition, the trial coordinator will maintain regular contact with the collaborators and, once they are in post, with the research nurses. The TMG will feedback to investigators and other stake-holders at the Investigators' meetings.

13.4.2 Trial Steering Committee

The purpose of Trial Steering Committee is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice and other relevant regulations. The TSC will agree on and sign off the trial protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial. The TSC's remit will include reviewing recruitment, data completeness, and protocol deviations. A vital role of TSC is to review recommendations from DMC, and help with the decision-making that follows on from the recommendations of the DMC.

The TSC has an independent chair: Professor Bhattacharya, an internationally recognised clinical researcher. The other members will include other independent members, Trial manager, Chief Investigator, Statistician and Ms Ruth Bender-Atik (Director of Miscarriage Association). The TSC will meet twice a year (either face-to-face or via teleconferencing) or more often if required.

13.4.3 Independent Data Monitoring Committee

Please also see Section 10.3.
The primary role of a DMC is to review the accruing trial data and to assess the safety data to make recommendations on whether the trial should continue, be modified or be terminated. In addition, the DMC will also examine effectiveness data to determine if continuation of the trial is unethical, and examine the recruitment, loss to follow-up, compliance, protocol violation data to ascertain if continuation of the trial is futile.

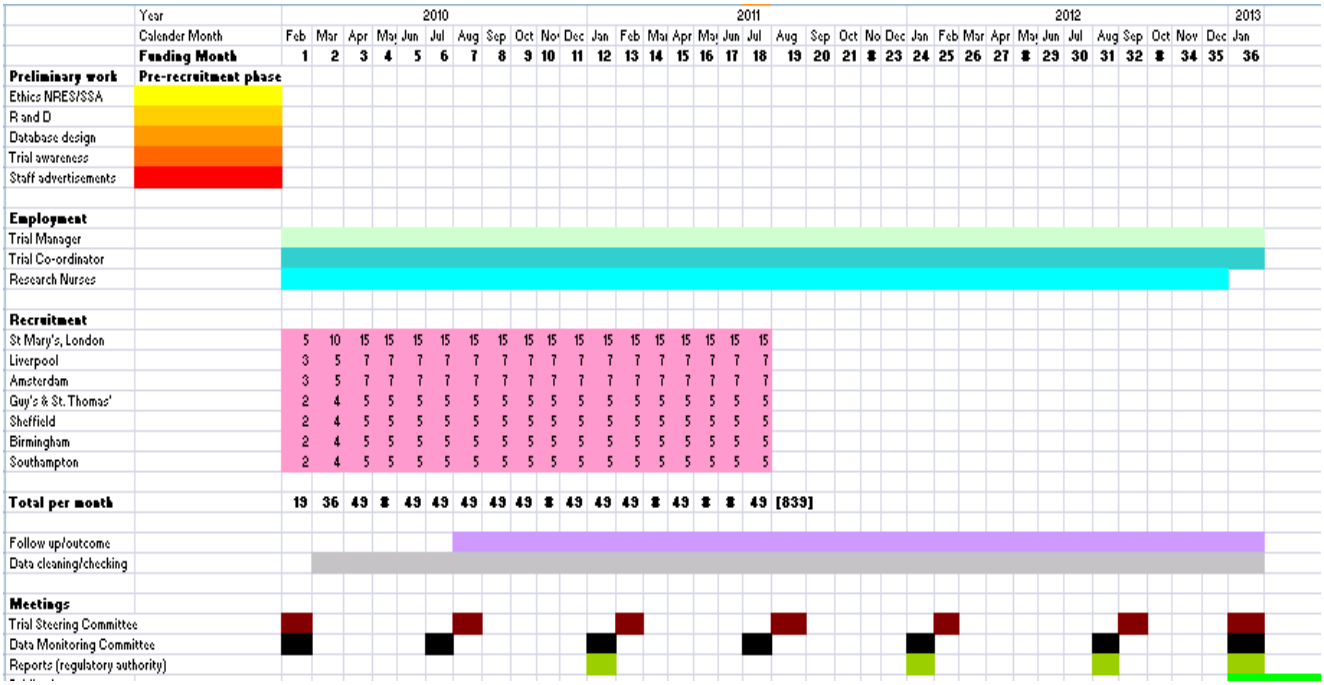
The PROMISE DMC has an independent chair: Dr Jennifer Kurinczuk, Reader in Perinatal Epidemiology and Deputy Director National Perinatal Epidemiology Unit, University of Oxford. All members of the DMC have no important financial or intellectual conflict of interest. The initial meeting of the DMC will be face-to-face meeting, in which protocol will be reviewed, and operating procedures for the DMC will be finalised. Subsequent meetings will be held either face to face or using teleconferencing technology.

Each DMC meeting will have four components: 1) closed meeting for the members of DMC only, to review recruitment, baseline characteristics, effectiveness, safety, missing data and protocol violations. These data will be prepared by the primary trial statistician. The study groups will be masked and identified as "A" and "B". b) open meeting of DMC with the chair of TSC, CI, TM, sponsor or funder, as appropriate. The purpose of this meeting is to access relevant information c) closed meeting for members of DMC to consider the issues from the open meeting and d) Meeting with TSC chair or CI or TM to convey the results and recommendations of the meeting.

Minutes from the open meeting will be available to all investigators and relevant stake-holders. Minutes from the closed meeting will be archived by the DMC chair and the trial statistician, and would only be available after the closure of the trial.

13.5 Timelines and targets

It is anticipated that the trial will last for 3 years, starting in Feb 2010. The GANTT chart below provides the details, including the anticipated recruitment number from each participating centre. We have extended the funding for the PROMISE trial. The new date to end randomisation is August 2013 and the last follow-up date is June 2014.



Audits of RM clinics at the 7 original centres show that >2,200 new recurrent miscarriage patients per year are seen in these centres. Audits again confirm over half of these women will be found to be eligible for the trial (i.e. a diagnosis of *unexplained* RM). Based on our previous experience, we expect up to 75% of eligible women to agree to participate; however, we have opted for a conservative recruitment rate of only 50% of eligible patients. The GANTT chart has been carefully scrutinised by the principal investigators and their teams in each centre to ensure the anticipated numbers are feasible in their centres. A first publication will be expected within four years of trial commencement.

13.6 Site responsibilities

The PROMISE trial will need to be conducted strictly in accordance with the most recent version of the authorised PROMISE Trial Protocol. The PROMISE Trial Protocol will need to be signed by the Principal Investigator for a participating institution on behalf of all staff who will be working on the PROMISE trial at that site (please see sections 16a and 16b). A favourable Site Specific Assessment (SSA) and R&D approval for the site is also required before recruitment

can begin. In addition, and in compliance with ICH GCP, all institutions participating in the trial will complete a delegation log and forward this to the Trial Co-ordinating Centre (TCC). Each person working on the PROMISE trial must complete this log and indicate their responsibilities. The TCC should be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Trial Master File at the institution and also at the TCC. A CV of all the trial staff and confirmation that he/she holds an honorary or substantive contract with the Trust in which the participating institution sits will also be necessary. It is mandatory that the principal investigator and any research nurses or doctors specifically employed to conduct the PROMISE Trial have GCP Training.

New centres wanting to participate in the study should contact the TCC.

14 Ethical, Regulatory and Research Governance Considerations

14.1 Ethical Issues

Ethical approval will be obtained before recruitment starts.

The primary ethical issue is the administration of a drug without full knowledge of its effects, although the existing evidence (section 4.3.1) suggests a large potential benefit. We believe there is true equipoise as to whether the intervention is beneficial (section 4.2). Furthermore, there is overwhelming support from the patients (83/88=94% agreeing to take part in the study) and the representatives of patient bodies (Miscarriage Association and the RCOG Consumer Forum) for this trial. There is substantial evidence of safety of progesterone in pregnancy (section 4.3.2), and progesterone is already in widespread use in pregnancy for other indications (e.g. IVF practice[8], prevention of preterm birth[13]). However, we will put in place robust mechanisms for addressing potential adverse events. All participants will be asked to report adverse events to their local research nurse; if the local trial nurse is unavailable for any reason, they will be able to report the events to the trial manager or trial co-ordinator who will be accessible on a mobile telephone 24 hours a day. In an emergency, the trial manager or another suitably qualified person appointed by the trial manager will be able to break the code and reveal the allocation if appropriate clinical management was thought to depend upon the knowledge of the pessary content. All adverse events will be captured be made available to the DMC.
The second issue of the potential for distress, discomfort, and inconvenience was explored during our interviews and consultations with patients and representatives of patient societies. It emerged that the likely distress, discomfort and inconvenience from the trial are limited, and would be of an acceptable level to most women. The issues raised were:
1. The vaginal route may be unacceptable for a small minority of women. In this event, the woman will have the option of receiving her intervention via the rectal route. There is pharmacological evidence that this route delivers an effective dosage and the manufactures of progesterone pessaries and the BNF recommend the rectal route as an alternate.
2. Face-to-face interviews (at the recruitment stage) may prolong the clinic visit by 30 - 45 minutes. This delay was felt to be well within acceptable limits by patients and patient society representatives.
3. Five or more telephone interviews: although this could be viewed as intrusive, the patients and patient society representatives felt this would be acceptable if certain precautions are taken. The suggested precautions (which are incorporated into the trial conduct) included: a) enquiring at the beginning of the telephone call if it was a convenient time to conduct the interview and if not, arranging to call at an alternative time; b) specifying the purpose and the expected duration of the

call; c) not leaving any messages if the phone is answered by anyone other than the index patient or if the phone enters an answer-machine mode; d) not calling at the woman's work-place if this can be avoided. Interestingly, most patients felt the phone calls would be re-assuring rather than intrusive, especially since the research nurse is likely to be able to help with the woman's standard care, for example, by facilitating the booking of ultrasound scans. In summary, we believe that the anticipated benefits outweigh the potential risks for the patients.

Our patient information sheet was produced in full consultation with patients and representatives of patient societies. The trial steering committee (TSC) and main Ethics Committee will approve the final version. We will keep up to date with the literature and amend the leaflet (and resubmit to TSC and ethics committee) if any important information comes to light.

14.2 Insurance and Indemnity

Imperial College London will provide negligent and non-negligent harm insurance. Arrangements for insurance and/or indemnity to meet the potential legal liability of the sponsor (Imperial College London) for harm to participants arising from the design, conduct, and management of the research will be provided by the Imperial College London. Imperial College London holds a policy with Zurich Municipal in the event of harm where no legal liability arises.

14.3 Data Handling and Data Protection

The trial has been designed (and will be conducted) to meet the requirements of:

- The Data Protection Act, 1998
- The NHS Code of Confidentiality, and
- The Caldicott Principles

The custodian for the data will be Dr A Coomarasamy.

Individual participant information obtained as a result of this study is considered confidential. Each participant will be allocated a unique study number at recruitment. All documents will use this as the identifier. Identifying and contact data will be held in separate *local* pass-word protected databases (in compliance with local and national confidentiality and data protection standards), which would be linked to the main online study database (ITMS) via the unique study number. All data will be analysed and reported in summary format. No individual will be identifiable.

Data will be acquired and stored on secure NHS or University computers. Access to data will be restricted by usernames and passwords at two levels (the NHS and University computers require username and password for access; following this the Integrated Trial Management System will require a username and password to obtain access to data. The necessary trial data will be encrypted and transmitted outside the NHS or university setting (for example to the DMC) only after anonymisation. No study data will be held in handheld media, laptops, personal computers, or other similar media.

The online database will be maintained according to the security policies of the Clinical Trials Unit (MFRU) at King's College London University. These cover assignment of passwords, encryption, database immediate back−up, off−site back−up and disaster recovery processes.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format. Paper-based data (e.g. signed consent forms) will be kept in locked filing cabinets at each site.

Although the proposed time period for retention of relevant anonymised clinical data is generally 15 years following the end of the study (according to the MRC guidelines), we will, in fact, store data for 25 years as obstetric outcomes are evaluated in our study. This would allow for review, reappraisal and any queries or concerns about the data, conduct or conclusions of the study to be resolved

Data generated as a result of this trial will be available for inspection on request by the participating physicians, representatives of the Sponsor, the ethics committees, host institutions and the regulatory authorities. This information is conveyed to the participants in the Patient Information Sheet, and permission is obtained in the Consent Form.

14.4 Funding

This study is funded by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) programme. No commercial funding will be sought for this trial. Participants will not be paid to take part in the trial, nor will they receive any incentives or other benefits.

14.5 Competing interests

None of the investigators, including the chief investigator, the trial manager and all the principal investigators from each site, have a financial conflict of interest. We will ensure that the members of TSC and DMC have no conflict of interest before they are invited to these bodies. All new staff will be asked to declare any conflict of interest.

15 Publication and Dissemination

The study design, conduct and findings will be published in a detailed HTA monograph (as required by the funder, NIHR-HTA, UK). Futhermore, the study findings will be presented at or published in:

- Peer-reviewed scientific journals
- National and International Conferences
- Trial specific website which will be maintained for at least 5 years after the end of trial (www.medscinet.net/promise), with links in the websites of participating organisations.
- We will submit the findings to patient representative bodies (e.g. Miscarriage Association)
- We will also submit the data to the Cochrane Collaboration for the updating of the existing review (Oates-Whitehead, 2003) with our trial data.

A "writing group" will be convened to take on the responsibility for writing the paper, and the publication will be in the name of "PROMISE Consortium". All investigators will be named, detailing their role in the study. The composition of the "writing group" will be decided following consultations between the TMG and TSC, and is likely to include the trial manager, chief investigator, statistician and high-accruing investigators.

Individual researchers must not publish data concerning their patients until the primary study question has been answered, AND explicit permission has been granted by the TMG.

16a Investigator Signature Page (Please send to TCC)

I have read and agree to the protocol, as detailed in this document. I agree to conduct this trial as detailed in this protocol. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP, EU Directive 2001/20/EC), the Declaration of Helsinki (1996) and the NHS Research Governance Framework and I agree to conduct the trial according to these guidelines.

I agree to allow trial-related monitoring, including audits, reviews and regulatory inspections by providing direct access to source data and documents as required. I agree to allocate my time and the time of my staff to aid with the monitoring.

I understand and accept that this study will be published under the authorship of "PROMISE Consortium", with all investigators listed. I agree that no separate publications are allowed without the consent of the Trial Management Group.

I agree to abide by the decisions made by Trial Steering Committee.

Principal Investigator's Name: ……...

Participating Centre's Name and Address: .....

.....

Signature: ……

Date: …….

The Principal Investigator should sign this page, detach it from the protocol, and send it to:

Dr A Coomarsamy
PROMSIE Trial Co-ordinating Centre
3rd Floor, Academic Department
Birmingham Women's Hospital
Metchely Park Road
Brimingham
B15 2TG
UK

16b Investigator Signature Page (Please retain for you records)

I have read and agree to the protocol, as detailed in this document. I agree to conduct this trial as detailed in this protocol. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP, EU Directive 2001/20/EC), the Declaration of Helsinki (1996) and the NHS Research Governance Framework and I agree to conduct the trial according to these guidelines.

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I agree to abide by the decisions made by Trial Steering Committee.

Principal Investigator's Name: ……...

Participating Centre's Name and Address: .....

.....

Signature: ……

Date: …….

The Principal Investigator should sign this page, and leave it in the protocol, and retain the protocol in the Site File.

17 References

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(17) Regan L, Backos MJ, Rai R. The Investigation and Treatment of Couples with Recurrent Miscarriage (RCOG Green-Top Guideline 17). 2003.

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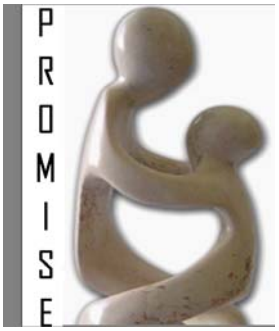
Appendix 1: Patient information sheet



Please insert Local Hospital Logo here.

PROMISE – Progesterone in Recurrent Miscarriage Study
Participant Information Sheet

We would like to invite you to take part in a research study. Whether you take part or not is entirely your choice. You do not have to take part, nor give a reason why you decide not to. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully.

We want to see whether progesterone hormone pessaries reduce the chance of a miscarriage in women who have previously had three or more miscarriages. This study is called the PROMISE Trial; "PRO" referring to Progesterone and "MISE" referring to Miscarriage.

- Part 1 of this information sheet tells you the purpose of this study and what will happen to you if you take part.
- Part 2 of this information sheet gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is not clear or if you would like more information.

Part 1

What is the purpose of the study?
The purpose of this study is to find out whether treating women with history of recurrent miscarriage with progesterone, a natural pregnancy hormone, from the time of a positive pregnancy test until 12 weeks of pregnancy decreases their chance of miscarrying.

Why have I been invited?
You have been invited to take part in the study as you have a history of recurrent miscarriage for which no underlying cause has been found.

Do I have to take part?
No. It is up to you whether or not you take part. If you wish to take part, you will be given this information sheet to keep and will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your medical care or maternity care in any way.

What will happen to me if I take part?
If you decide to take part in the study, and have signed the consent form, you don't need to do anything until you become pregnant (and have a positive urine or blood pregnancy test). Once this happens, we want you to let the research nurse know, by telephone as soon as possible. The phone number to call is given on the last page of this information sheet. You will probably be about 4 weeks pregnant (4 weeks from the last menstrual period) at this time. When the research nurse receives your call, she will ask you some details about this pregnancy and recheck your clinical history to make sure you are still eligible to take part in the study.

If you remain eligible, the nurse will arrange the study pessaries to be dispensed to you. You will be asked to take two pessaries – either vaginally or rectally -, twice daily (in the morning and at bedtime), from the time you receive them from us to 12 weeks of pregnancy (We will let you know when you need to stop taking the pessaries). These pessaries will either be progesterone or identical looking dummy pessaries. We do not know if progesterone will help reduce the risk of miscarriage at all, and that is why we need to compare women who take progesterone with others who take the dummy pessaries.

Whether you get the progesterone or dummy pessaries will be decided by a computer. The computer will allocate treatment randomly, like tossing a coin, to decide whether you should receive progesterone or dummy pessaries. You will have an equal chance of receiving progesterone or the dummy pessaries. You will not know which, and neither will the doctors, nurses or researchers looking after you (although they will be able to find out if they need to).

The research nurse will be able to get most of your pregnancy outcome data from your hospital notes. But she may need to contact you to complete the outcome data if these are not available in your or your baby's notes. We may ask you to come and see us so we can get all the information we need. We would also like your permission to follow up your baby's long-term health. At the conclusion of the study, we will let you know of the findings through your preferred method of contact.

What will I have to do?

All you have to do is to keep the pessaries in a safe place, and take 2 pessaries in the morning and 2 pessaries in the evening. It is not necessary to take the pessaries at exactly the same time every day. If you forget to take the pessaries, don't worry. If it has been less than six hours from when you would have normally taken it, please take the pessaries as soon as possible, and continue the rest of the pessaries as usual. If it has been more than six hours from when you would have normally taken the pessaries, please omit these pessaries, and take the next lot of pessaries at the usual time.

In the event of you losing the pessaries, please let us know, and we will get you a further supply of the same type of pessaries as soon as possible.

You will be given enough vaginal pessaries to last you until 12 weeks of pregnancy. Each packet will contain enough pessaries for 4 weeks (112 pessaries). At the end of each 4 weeks, please post back the packet, either empty or with any unused pessaries. You will be given free-post envelopes to post the packets back to your hospital. Your research nurse will contact you by telephone to make sure everything is okay if you do not return the packets. If you lose your envelopes, please use another and write the freepost address, making sure your study number is on the envelope. That way you won't need a stamp.

What is the drug being tested?
We are testing progesterone hormone pessaries (versus a dummy pessaries), at a dose of 400mg (two pessaries at 200mg each), twice daily. Progesterone is a naturally occurring female hormone. It is commonly used in IVF (test-tube baby) practice and to prevent preterm birth.

What are the other possible disadvantages and risks of taking part?
Side effects with progesterone pessaries are rare or minor. Previous studies on natural progesterone treatment did not report any serious side-effects to the mother or the baby. However, reported side effects of progesterone include fluid retention, bloating, headache, sleeplessness, diarrhoea and jaundice. We do not anticipate any problems for those taking part in this study. If you have any concerns, please contact the research nurse (details on the last page of this information sheet). If you become unwell, please contact your general practitioner, accident and emergency services, or ambulance services, as appropriate.

What are the possible benefits of taking part?
We do not know if the study will help you personally, but the information we will get may help improve the pregnancy outcome for women in the future.

How is progesterone administered?

Both the progesterone and the placebo (inactive drug) are in the form of pessaries (capsules). We would ask you to give yourself two capsules twice a day ideally by placing them in the vagina – rather like using a tampon. Alternatively, you can use the capsules as suppositories – inserting them into the rectum.

What if there is a problem? What if something goes wrong?
If you have a complaint about the way you have been treated during the study or any other matter, you can make a complaint. There is more detailed information in Part 2 of this leaflet.

Will my taking part in this study be kept confidential?
Yes. The study will follow ethical and legal practice and all the information about your participation in this study will be kept confidential. Details about this are included in Part 2 of this leaflet.

This completes part 1 of the information sheet.
If the information in Part 1 has interested you and you are considering participating, please read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. If this happens, we will tell you and discuss whether you should continue in the study. If you decide not to carry on, we will make arrangements for your care to continue. If you decide to continue in the study we may ask you to sign an updated consent form.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I do not want to carry on with the study?
If you decide to take part and then change your mind you are free to withdraw at any time without giving a reason (although it would be useful to know why) and your treatment will not be affected in any way.
If you withdraw from the study, we will ask your permission to keep in touch with you to know the outcome of your pregnancy and to use such information in our analysis.

Keeping in contact

Until 12 weeks of pregnancy, you will be seen at your normal early pregnancy / miscarriage unit at regular intervals according to local policy. After this time, the research midwife will contact you by telephone at 20 / 26 / 34 / and 38 weeks of pregnancy. The purpose of these telephone calls is to maintain contact and to enquire regarding the progress of your pregnancy. Such questions, which would have been routinely asked at your antenatal visits, may include specific enquires as to whether you have experienced any complications such as issues regarding blood pressure and growth of the baby. It is important to state that at all times the management of your pregnancy rests with the obstetricians and midwives at the hospital at which you have booked for antenatal care and delivery.

After delivery

After delivery, we will ask your permission to contact the hospital at which you delivered to obtain data on the outcome of your pregnancy (including any complications you may have had); the gestation at delivery; mode of delivery; baby's sex and birthweight and any complications the baby may have had after delivery.

What if there is a problem?
Complaints

If you have a concern about any aspect of this study, you should ask to speak to the local research nurse or doctor who will do their best to answer your questions (contact details can be found at the end of this information sheet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital. You can contact the Patients Advisory and Liaison Service (PALS) or you can write to the Chief Executive of the hospital. You have the same rights whether or not you take part in this study.

Harm

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. Adverse pregnancy outcomes (for example miscarriage or stillbirth) not directly related to study medication or conduct will not be eligible for compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Mr Raj Rai, Imperial College London). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Governance Office.

Will my taking part in this study be kept confidential?

Yes. All information collected from you for the purposes of this study will be kept strictly confidential in the same way as your medical records. Any information used outside the hospital or university will have any identifying details removed so that your data remains completely anonymous. All information will be held securely and in strict confidence. You will not be identified in any publication of results from this study. Occasionally, inspections of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But apart from this, only study organisers will have access to the data.

Involvement of your General Practitioner

We will inform your general practitioner of your participation in the study if you agree.

What will happen to the results of the research study?

When the results of the PROMISE study are known, we will inform you of the overall results of the study as well as which pessaries you were taking (through your preferred method of contact). We will also publish the results of the study in

medical journal(s). We will make the information available on our website for the general public.

Who is organising the research?

The research is organised by Imperial College, London, UK, and managed and co-ordinated by University of Birmingham, UK. No private companies are involved in the organisation or management of this study.

Who is funding the research?

The National Institute for Health Research (NIHR) have funded this study. The research nurses working on this project have their salaries paid by this organisation. The other nurses and doctors do not receive any payment if you help with this research.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable ethical opinion by West Midlands Research Ethics Committee.

Do you have any further questions?

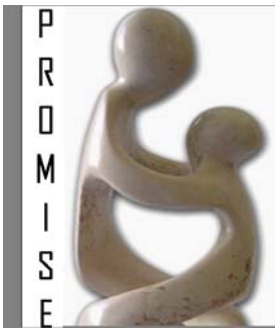
Having read this leaflet and discussed with the research nurse or doctor, we hope that you will choose to take part in the PROMISE study. If you have any questions about the study now or later, please feel free to ask your nurse or doctor, or contact the research nurse at xxxxxxxxxxxx, or the Trial Manager at 0121 623 6835

The UK Clinical Research Collaboration has produced a guide entitled, 'Understanding Clinical Trials'. This can be downloaded from their website: www.ukcrn.org.uk and could be useful if you require general information about research.

You will be given a copy of the information sheet and a signed consent form to keep.

Thank you for taking time to read this sheet and for considering taking part in the study.

Appendix 2: Consent form



Please insert Local Hospital/Centre details and Logo here.

PROMISE – Progesterone in Recurrent Miscarriage Study

Chief Investigator: Dr Raj Rai, Imperial College, London

CONSENT FORM

Please initial the boxes below

1. I have read the information sheet for the PROMISE study (version 5, dated 14/10/2009) and have had the opportunity to consider the information, ask questions, and have these answered satisfactorily. ☐
2. I understand that participation in this study is entirely voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care being affected. ☐
3. I understand that my medical notes will be looked at by members of the research team, and by regulatory bodies auditing research practice. ☐
4. I consent to taking part in the PROMISE study, which will require me taking the study pessaries vaginally or rectally. ☐
5. I agree to face-to-face and telephone interviews to gather the outcome data from the study. ☐
6. I consent to gathering of data from my baby following his/her birth. ☐
7. I agree to my baby being followed up in the future, and understand this may involve tracing through NHS databases and GP records. ☐
8. I agree to my GP being informed of my participation in the study. ☐

Name……Date of Birth……Hospital ID……

Address……..

Signed

(Participant)_____Date_____

Signed (Research Nurse/midwife/doctor)_____Date_____

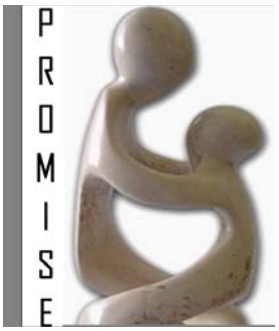
Print name (nurse/midwife/doctor)_____

Signed (witness, where appropriate) _____Date_____

When completed:

- 1 form for participant
- 1 for researcher site file
- 1 (original) to be kept in medical notes.

Appendix 3: GP letter template



Please insert Local Hospital Logo here.

Dr
Address

Date:
RE:

Dear Dr
This lady has kindly agreed to participate in the PROMISE Trial (A multicentre randomised placebo-controlled trial of progesterone in spontaneously conceived women with a history of unexplained recurrent miscarriages). The study is funded by the NIHR – HTA programme, and has an ethical approval from West Midlands Research Ethics Committee.

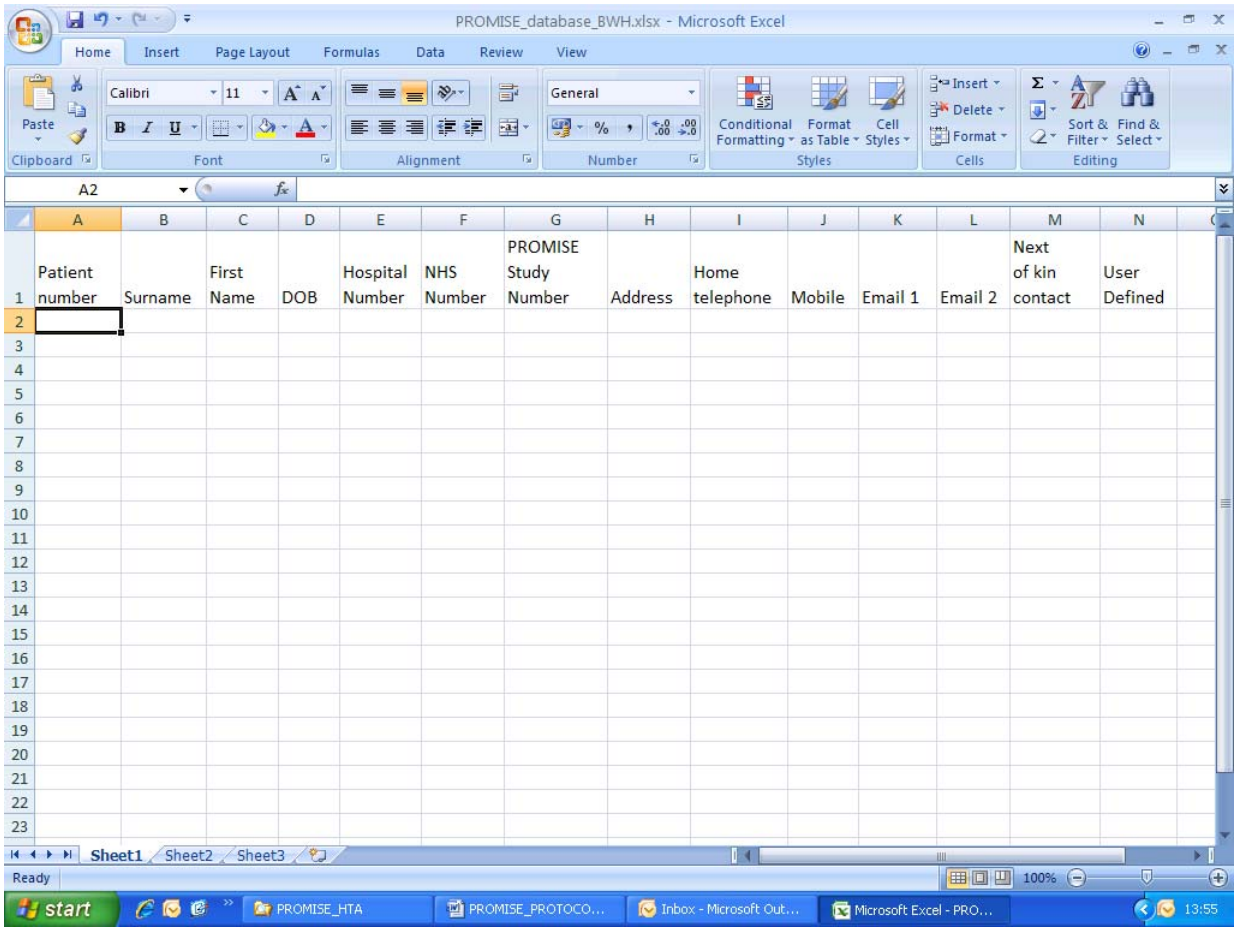
Your patient will be randomised to take either progesterone pessaries (400mg twice daily) or identical placebo, from the time of diagnosis of pregnancy to 12 completed weeks of pregnancy. Since this is a double-blind study, neither the participant, nor the investigators will know which treatment your patient has been allocated to. Your patient has the contact details for the research nurse in case of difficulties.

We do not anticipate that your patient's participation in the study will impact on your care of her, and we will not ask you to carry out any study related investigations or interventions.
This letter is for information only.

If you wish any further details, please feel free to contact either myself or the research nurse for the study [research nurse name and contact]. A copy of Patient Information Leaflet for PROMISE trial is enclosed.
Thank you for your support,
Yours sincerely,

Dr Arri Coomarasamy, MBChB, MD, MRCOG
Trial Manager for PROMISE Study.
Consultant Gynaecologist, and sub-specialist in Reproductive Medicine
University of Birmingham, UK.
Email: a.coomarasamy@bham.ac.uk Tel: +44 (0) 121 623 6835
GMC: 4219367

Appendix 4: Structure of database of identifying and contact information to be held locally.



Appendix 5: Sample trial drug label

For Clinical Trials Use Only
PROMISE Trial
Eudract Number: 2009-011208-42
224 capsules of Progesterone 200mg or Placebo.
Batch #: 09EC001
Expiry: MM/YYYY

Attach Patient Label Here (with Patient Name, Date of Birth, and Identification number)

How to take: For vaginal use. Please insert the tablets as high up in the vagina as possible.
How much to take: Please insert two tablets in the morning and two tablets at bedtime.

Code Number: 1xxx

Precautions: Keep out of reach of children. Store at 15°C – 25°C / 59°F – 77°F

MA Holder/ Manufacturer (M07/196): Laboratoires BESINS INTERNATIONAL, 3, rue du Bourg l'Abbé, 75003, Paris, France
Study Sponsor: Imperial College, London, W2 1PG
Tel: *+44(0)207 594 1188*
Chief Investigator: Dr Raj Rai, Imperial College, London W2 1PG
Tel: *+44(0)207 594 1188*

Appendix 6: Serious Adverse Event Reporting *(Note: These two pages are "image" files; clear "text" files can be down loaded from the trial website: www.medscinet.net/promise)*

Imperial College London

PROMISE Trial

Serious Adverse Event Reporting Form

EudraCT number: 2009-011208-42

Please fax to 0044(0)121 623 6835 within 24 hours of notification of event ***FAO: Dr Arri Coomarasamy***

Patient Initials: ..... Patient Study No: ☐☐☐☐☐☐☐☐

Patient Hospital Number: ..... Date of Birth: ☐☐ ☐☐ ☐☐☐☐ (d d m m m y y y y)

Treating Clinician: ..... Hospital: .....

Type of Report ☐ 1=First 2=Interim 3=Final

Trial Arm ☐ 1= 2=

Sex ☐ 1= Male 2= Female

Height ☐☐☐ cm

Weight ☐☐☐.☐ kg

Date of last trial treatment given prior to SAE ☐☐ ☐☐ ☐☐☐☐ (d d m m m y y)

Was the trial treatment given at full protocol dose prior to event? ☐ 0= No, specify..... 1=Yes

Why was the event serious? *(choose most serious)* ☐
1= Resulted in death
2= Life-threatening
3= Required inpatient hospitalisation or prolongation of existing hospitalisation
4= Resulted in persistent or significant disability/incapacity
5= Resulted in congenital anomaly/birth defect
6= Other medically important event

Where did the SAE take place? ☐
1= Hospital
2= Out-patient clinic
3= Home
4= Nursing home
5= Hospice
6= Other, specify.....

Describe SAE (*include relevant symptoms, body site, and relevant lab tests, treatments received)*
continue on a separate sheet if necessary

Details of SAE

Serious Adverse Event Name:	**Duration of SAE** (dd mmm yy)	**SAE Status** 1= Resolved 2= Resolved with sequelae 3= Persisting 4= Worsened 5= Fatal 6= Not assessable	**Expectedness** 1= Expected* 2= Unexpected
Name	Date of Onset ☐☐ ☐☐☐ ☐☐☐☐ Date Resolved ☐☐ ☐☐☐ ☐☐☐☐ or tick box if ongoing ☐	☐	☐

** Was the event one of the recognised undesirable effects of the trial medication?*

Trial Treatment

Trial drugs patient was receiving when SAE started	**Total Daily Dose**	**Start Date of Most Recent Cycle** (dd mmm yy)	**Currently Ongoing?** 0= no 1=Yes	**End Date** (dd mmm yy)	**Causal relationship to event** 1=Definitely 2= Probably 3= Possibly 4= Unlikely 5= Not related 6=Not assessable	**Action Taken** 0=None 1=Dose reduction 2=Treatment delayed 3=Treatment delayed and reduced 4=Treatment permanently stopped
		☐☐ ☐☐☐ ☐☐☐	☐	☐☐ ☐☐☐ ☐☐☐	☐	☐
		☐☐ ☐☐☐ ☐☐☐	☐	☐☐ ☐☐☐ ☐☐☐	☐	☐
		☐☐ ☐☐☐ ☐☐☐	☐	☐☐ ☐☐☐ ☐☐☐	☐	☐
		☐☐ ☐☐☐ ☐☐☐	☐	☐☐ ☐☐☐ ☐☐☐	☐	☐

Patient's Study Number ☐☐☐☐☐☐☐☐

Other treatments at time of event (include concomitant medication, radiotherapy, surgery, palliative care, continue on a separate sheet if necessary) Exclude any therapy given for management of SAE

Treatment Give generic name of drugs/treatment given in the last 30 days.	**Total Daily Dose**	**Route of Administration** 1=Oral 2=Intravenous 3=Subcutaneous 4=Other, specify	**Start Date** (dd mmm yy)	**Currently Ongoing?** 0= no 1=Yes	**End Date** (dd mmm yy)	**Action Taken** 0=None 1=Dose reduction 2=Treatment delayed 3=Treatment delayed and reduced 4=Treatment permanently stopped
			☐☐ ☐☐☐ ☐☐	☐	☐☐ ☐☐☐ ☐☐	☐
			☐☐ ☐☐☐ ☐☐	☐	☐☐ ☐☐☐ ☐☐	☐
			☐☐ ☐☐☐ ☐☐	☐	☐☐ ☐☐☐ ☐☐	☐
			☐☐ ☐☐☐ ☐☐	☐	☐☐ ☐☐☐ ☐☐	☐

Other relevant information to facilitate assessment
(Include medical history, drug or alcohol abuse, family history, findings from special investigations)

Was this event expected in view of the patient's clinical history?
☐ 0= No
1= Yes

Additional Information:

Signature
Authorised Health Professional ……

Print name……

Date of report ☐☐ ☐☐☐☐☐ ☐☐ (d d m m m y y)

Contact telephone no……

OFFICE USE ONLY

Was SAE drug related? Yes☐ No☐

Was event unexpected? Yes☐ No☐

Was the event a SUSAR? Yes☐ No☐

Date sent to MHRA ☐☐ ☐☐☐ ☐☐ (d d m m m y y)

Date entered on database ☐☐ ☐☐☐ ☐☐ (d d m m m y y)

MEDRA code ☐☐☐☐☐☐☐☐

Event No ☐☐☐☐☐☐☐

Comments:

Form checked by TCC staff (signature) ……

Date ☐☐ ☐☐☐ ☐☐ (d d m m m y y)

Checked by clinical reviewer (signature) ……

Date ☐☐ ☐☐☐ ☐☐ (d d m m m y y)

Appendix 7: Sample screen-shot of Integrated Trial Management System (ITMS) that will be used for complete Electronic Data Capture.

ITMS will allow:

1. Entry of baseline data
2. Eligibility checking
3. Minimisation Randomisation
4. Outcome data collection (Electronic CRF – case report forms)
5. Data cleaning
6. Real-time global monitoring of recruitment, site by site
7. Automated alerts for missing outcome data
8. Preparation of reports for DMC and TSC
9. Unique Adverse Event procedures for prompt and appropriate actions
10. Complete audit trails
11. Powerful engine for query generation