Academic and Clinical Central Office for Research and Development

A randomised controlled trial to determine the effectiveness of bridging from emergency to regular contraception: The Bridge –it study

Study Protocol

A randomised controlled trial to determine the effectiveness of bridging from emergency to regular contraception: The Bridge –it study

BRIDGE-IT

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Funder	HTA/NIHR
Funding Reference Number	*15/113/01*
Chief Investigator	Professor Sharon Cameron
REC Number	17/SS/0080
ISRCTN Number	70616901
Version Number and Date	3, 16.04.18
Amendment classification and number: **Non-substantial amendment 16th April 2018**	Summary of change(s) Minor clarification to page 14 of protocol

COORDINATING CENTRE

Chief Investigator Dr Sharon Cameron Tel: 0131 536 2091 Fax: Email: Sharon.cameron@ed.ac.uk	**Co-sponsor Representative** Tel: Fax: Email:
Trial Manager Claire Battison Tel: 0131 651 9919 Fax: Email: c.battison@ed.ac.uk	**Trial Statistician** Professor John Norrie Tel: 0131 651 7895 Fax: Email: john.norrie@ed.ac.uk

Co-I Prof Anna Glasier Tel: Fax: Email: anna.glasier@ed.ac.uk	**Co-I** Dr Lisa Mc Daid Tel: Fax: Email: Lisa.McDaid@glasgow.ac.uk

Co investigators

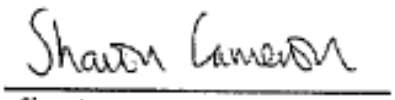
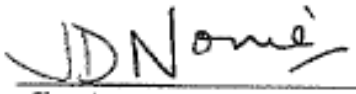
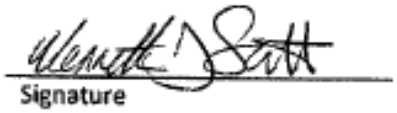
Tayside **Principal Investigator** Andrew Radley Tel: Fax: Email: Andrew.radley@nhs.net	**London, (central)** **Principal Investigator** Prof Judith Stephenson Tel: Fax: Email: judith.stephenson@ucl.ac.uk
London (south) **Principal Investigator** Dr Paula Barraitser Tel: Fax: Email: paula_baraitser@mac.com	Tel: Fax: Email:

CONTENTS

PROTOCOL APPROVAL

Bridge-it

Signatures

Dr Sharon Cameron Chief Investigator	 Signature	16/06/2017 Date
Prof John Norrie Trial Statistician	 Signature	03/10/2017 Date
Kenny Scott Sponsor(s) Representative	 Signature	04/10/17 Date

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
CHaRT	The Centre for Healthcare Randomised Trials
CI	Chief Investigator
EC	Emergency contraception
DMC	Data Monitoring Committee
DOH	Department of health
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISD	Information Services Division
ISF	Investigator Site File
LARC	Long-acting reversible contraception
LNG	Levonorgesteral
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PGD	Patient Group Direction
PI	Principal Investigator
PIS	Patient information Sheet
POP	Progesterone Only Pill
PPI	Patient and Public Involvement
PPI	Patient Public Involvement
QA	Quality Assurance
RA	Rapid access
R&D	Research and Development
REC	Research Ethics Committee
RTC	Randomised Controlled Trial
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SRH	Sexual and Reproductive Health
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering committee
UAR	Unexpected Adverse Reaction

SUMMARY

Design: A cluster randomised crossover trial; community pharmacies will be cluster randomised to provide the intervention followed by control phase (on a new group of women) or vice versa.

Setting: 26 community pharmacies in Scotland and England (Edinburgh, London and Dundee).

Target Population: The community pharmacist will assess medical eligibility of women (≥16 years) presenting for emergency contraception (EC) and provide EC according to normal practice.

Health technologies being assessed: The intervention consists of provision of a 3 month supply of the progestogen only pill (POP) (75 mcg desogestrel) (following a patient group direction (PGD)) to be started the day after EC (1.5 mg levonorgestrel) as a temporary (bridging) method of contraception, together with expedited access to a local Sexual and Reproductive Health (SRH) service as a drop-in for advice and provision of effective contraception; including long-acting reversible (LARC) methods (i.e. implant, intrauterine and injectable). Standard care: usually comprises verbal advice to visit a GP or SRH service with/without written information but will be characterised by a mystery shopper study undertaken in participating pharmacies before this phase of the trial starts.

Methods: In the intervention phase, pharmacists will provide women with the POP and instructions for use, and advise women that upon presentation of their study card to the local SRH service that they will be seen as a drop in for ongoing contraception. In the control phase, pharmacists will advise women to attend their GP/ SRH service/ usual contraceptive provider for ongoing contraception (standard care).
All women (women in control arm and women in intervention arm) will complete a short questionnaire via telephone with a research nurse at 4 months after attendance for EC and again at 12 months. If women prefer this can be a self-completed survey by text /email or post.
A process evaluation of the intervention will be conducted to access implementation, fidelity and reach. This will contribute to evaluating the effectiveness of the intervention, by assessing what was delivered, how it was delivered, and what role context may have in shaping the delivery and outcomes to inform future implementation. The process evaluation will comprise of quantitative and qualitative data collection, including: review of training and observation materials; observation of training; protocol adherence checklists and recruitment and monitoring forms (to be completed by pharmacists); semi-structured telephone interviews with participants (n=60), pharmacists (n=26), and SRH service providers (n=12); audit of local contraceptive services within 10 miles of study sites in London, Edinburgh and Dundee; and monitoring of contemporaneous events, such as relevant high coverage media stories using Google Alerts.

Outcomes:
Main outcomes are (i) Effective contraception use (hormonal and intrauterine) at 4 months (in intervention vs standard care) determined by telephone contact at 4 months or by text/email/post (when POP supply will have run out) (ii) LARC use in both arms at 4 months, (iii) Proportion having undergone an abortion at 12 months using record linkage from participants to national registries

Secondary outcomes: (i) Effective contraception use (in intervention vs standard care) determined by telephone contact at 12 months (ii) LARC use in both groups at 12 months (iii) Proportion with unintended pregnancy at 12 months (self-reported- using validated tool the London measure of Unintended Pregnancy) (iv) Process evaluation of the intervention implementation, fidelity and reach (to understand why/why not the intervention works and to inform future roll out/implementation) (v) Cost effectiveness.

Adverse events following EC and EC/POP will not be recorded. SAEs that are related to the intervention will be collected.

1. INTRODUCTION

1.1 Background

Unintended pregnancy is a major public health problem. Despite having among the highest rates of modern contraceptive use worldwide, the UK has among the highest abortion rates in Europe (1). In 2014 almost 200,000 pregnancies ended in induced abortion (2,3). Unintended pregnancy also ends in childbirth; around 10% of UK births are unintended and 25% mistimed (4). Unintended pregnancy is costly to the NHS (5) and distressing for women. Unintended pregnancies are over represented in young women from deprived backgrounds. Unintended childbirth can have both socioeconomic consequences for women and their families and mental health consequences (6).

EC prevents pregnancy in individual women following unprotected sex or contraceptive accidents (e.g. burst condom). Approval of EC from pharmacies *and* making it free of charge to *all* women in Scotland and Wales and free to many women in England, has increased use and indeed EC is now largely obtained from pharmacies (7). But whilst trials have shown that facilitating access to EC increases use of EC, they have failed to show an effect on unintended pregnancy rates (8).

EC (levonorgestrel 1.5 mg) is only effective if taken within 72 hours of unprotected sex; it does not prevent conceptions from subsequent acts of sex. The risk of pregnancy is increased up to threefold among women who have further unprotected sex in the same menstrual cycle after using EC (9). An effective method of contraception should therefore be started as soon as possible (10). However the only contraceptives available from pharmacies without prescription are condoms, which have high failure rates. To start an effective contraceptive women must see a doctor/nurse – and many do not.. In addition, in one UK study fewer than half of pharmacists gave advice about ongoing contraception after EC (11).

In a pilot study which we undertook in 12 pharmacies in Edinburgh (12), 168 women presenting for EC were randomised to receive one month of a POP; rapid access (RA) to a local SRH service; or standard care. Participants were contacted by telephone 6-8 weeks later to determine current contraceptive use. 35/ 39 women in the POP arm (90%) used the pills provided and 9/ 28 women (32%) in the RA arm attended the SRH clinic. Compared to standard care, the proportion of women using effective contraception 6-8 weeks after EC was significantly greater in both the POP (56% vs. 16% p=0.001) and the RA groups (52% vs. 16% p=0.027). We concluded that supply of one month of POP after EC or RA from pharmacy to a SRH service might increase short-term uptake of effective contraception following EC.

We now propose a large definitive randomised trial to determine whether a pharmacy-based intervention designed to facilitate the uptake of effective contraception after EC increases use of effective contraceptive methods (including LARC) and reduces unintended pregnancy at one year when compared with standard care

1.2 Rationale for Study

Unintended pregnancy remains a public health problem in the UK. Guidance from the Faculty of Sexual and reproductive healthcare stresses the need to 'quick -start' ongoing contraception after EC (10). In 2014, NICE guidance on contraceptive services for young people has endorsed this recommendation (13).

In some parts of the UK pharmacies are offering women supplies of contraceptive pills after EC use despite no evidence that this reduces abortion rates or is cost effective. Our own published pilot study showed a significant increase in use of effective contraception 6-8 weeks after EC (12). Whilst use of an effective method of contraception at 6-8 weeks after using EC is a promising outcome of the intervention, it is not enough. Discontinuation rates of hormonal contraceptives are high – 40-50% during the first year of use (14). We need to show that the intervention reduces unintended pregnancies. If proven effective in reducing unintended pregnancy, we also need to know that the intervention is cost effective, before we can recommend adoption of this approach. A recent cost effectiveness analysis of EC estimated that in 2011 unintended pregnancies cost the NHS over £1 billion (5). We calculated that the average cost per unintended pregnancy was £1519 in direct pregnancy healthcare costs, rising to £1663 if child health costs in the first year are included and totalling £2922 for all healthcare and social costs of unintended pregnancy in 2011 (5). It is possible that these costs are an underestimate of the 'real costs', since they did not include the cost of managing medical complications of pregnancy or take account of additional costs associated with teenage pregnancy. Given this, it is likely that the cost of unintended pregnancy in the teenage population is even higher than our estimates of unintended pregnancy across all age groups. Women who present for EC should be given the best chance to prevent an unintended pregnancy. If the pharmacy-based intervention that we propose is shown to be cost effective, then this would confer savings for the health systems that could be invested elsewhere in health care.

2. STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

Our main aim is to develop a simple and affordable intervention which encourages/ facilitates the uptake of effective ongoing contraception among women obtaining EC from pharmacies thereby reducing unintended pregnancy. The objective of this proposed study is to test whether the proposed intervention can be used in pharmacies to facilitate uptake of effective ongoing contraception, and if so does it reduce the risk of unintended pregnancy as measured by abortion rates. The central hypothesis is that facilitating the uptake of effective ongoing contraception (hormonal or intrauterine) after use of EC will result in reduced unintended pregnancy rates.

The primary objective: to determine whether offering women attending a pharmacy for EC a 3 month supply of POP plus the offer to attend a local SRH service results in increased uptake of effective contraception whether the intervention reduces abortion rates:

(i) Effective contraception at 4 months, 12 months
(ii) LARC use at 4 months, 12 months

(iii) Abortion data (collected using record linkage to the national health databases) during the follow-up period of 12 months. The proportion undergoing an abortion within 12 months will be compared between women in the intervention arm and women in the standard care arm (odds ratio of abortion within 12 months intervention vs standard care).

2.1.2 Secondary Objective

(i) To assess of the practicality of the intervention (process evaluation to assess why this trial works (or not) for whom, and why)

(ii) To determine whether the intervention is cost effective to the NHS.

2.2 Endpoints

2.2.1 Primary Endpoint

- Odds ratio of using effective contraceptive method (hormonal or intrauterine) in intervention vs standard care at 4 and 12 months
- Odds ratio of using LARC method in intervention vs standard care at 4 and 12 months
- Abortion data (collected using record linkage to the national health databases) during the follow-up period of 12 months. The proportion undergoing an abortion within 12 months will be compared between women in the intervention arm and women in the standard care arm (odds ratio of abortion within 12 months intervention vs standard care).

2.2.2 Secondary Endpoints

- Process evaluation
- We will define a cost-effectiveness model that includes the cost of the intervention plus cost of contraception over the year plus cost of abortions.

3. STUDY DESIGN

A cluster randomised cross over trial involving 26 pharmacies in 3 UK regions (14 in London (South and Central), 8 in Lothian (Edinburgh and region) and 4 in Tayside (Dundee and region) recruiting a total of 2080 women presenting for EC. Each pharmacy will be expected to recruit 80 women to provide 60 evaluable women (30 in each period, and allowing for a 25% loss to follow up at 12 months).

Before the trial starts, a mystery shopper study undertaken in participating sites will characterise standard care (usually verbal advice to visit a doctor for contraception, with/without written information).

3.1 The Mystery Shopper Exercise

The purpose of the mystery shopper exercise is to define 'standard care' in the control phase. The mystery shoppers and the scenario used will be chosen by the Patient Public Involvement (PPI) team (for example see **Appendix 3**).

A simple scenario will be used (but adapted/changed) (Appendix 3). Immediately after leaving the pharmacy the mystery shopper will complete a standard data collection proforma, recording any information/advice given by the pharmacist about use of contraception after taking EC, including provision of the written information on contraception. The approach will be rehearsed with and approved by the PPI group.

Two mystery shopper visits will be undertaken in each participating pharmacy during the month before the pharmacy begins participation in the **contro**l arm of the study.

Should any problems with study performance arise in any pharmacy during the course of the study the mystery shopper could be used to assess pharmacy practice and this would be fed back to the pharmacy to ensure standard care was of agreed 'standard'. Positive feedback will also be provided to participating pharmacies.

3.2 Intervention

The planned intervention is a composite intervention consisting of 3 months of POP **and** the offer to attend a local participating SRH service to discuss and provide ongoing effective contraception especially LARC methods (intrauterine contraceptive methods and contraceptive implants). LARC methods are the most effective methods at reducing unintended pregnancy (13). Uptake of LARC is significantly increased when LARC can be provided without delay (15) Three packets of POP, (75 mcg desogestrel; UK) containing 28 tablets will be provided (at no cost) to women as a bridging method of contraception, giving them three months within which they can attend their usual healthcare provider for on-going contraception. The POP has very few absolute contraindications (16) making it safer for pharmacy provision compared with the combined oral contraceptive pill. This particular POP has been chosen since it is the market leader. It is also the most effective POP (as it has high rates of ovulation inhibition) and inexpensive (£9 for 3 months of the generic version, British National Formulary costs 2016). Locally approved Patient Group Directions (PGDs) will permit participating pharmacists to dispense the supply of POP to women recruited to the study. Pre-study training will be undertaken with participating pharmacists including medical contraindications to POP, any potential drug interactions medications and missed pill guidance. Family Planning Association written information regarding the POP will be provided. Pharmacists will advise women to start the POP the day following intake of EC. Pharmacists will also advise women that they should either abstain or use additional barrier contraception for 48 hours, before relying upon the POP for contraceptive protection (10).
Pharmacists will encourage women to attend the participating SRH service to obtain the contraceptive method of their choice. Participants (intervention arm) will be given a study card to alert staff at SRH services that they are on the Bridge-It trial. This card will also provide written information about the location and opening hours of the local participating SRH service. The participating SRH premises are located within a 3-mile radius of the participating pharmacies and provide free services for all methods of contraception.

Each pharmacy will recruit on average 80 women to provide around 60 evaluable women at 12 months. 30 women will be recruited to the intervention arm and 30 women will receive standard care. In order for each pharmacy to recruit on average 80 women, pharmacies will recruit for approximately two months in each intervention or standard care phase; some pharmacies will recruit for a shorter or longer duration depending on the recruitment rate at the pharmacy and the size of the pharmacy. However, there will be a minimum break (wash-out period) of two weeks in between the two recruitment periods.

The order in which recruitment to the two arms is undertaken (intervention first or standard care first) will be randomised. Once all subjects have been recruited the pharmacist's role in the study will consist of participation in the process evaluation interviews only.

The research design is as close as possible to every day clinical practice. In undertaking our pilot study we learned much about doing research in pharmacies (17) and it is this experience and our collective knowledge and experience of interventions aiming to change contraceptive behaviour, which guides our approach to the research proposal.

Follow-up will be undertaken by research nurses. Women in both arms of the study will be contacted by telephone 4 months after obtaining EC (when supplies of study drug (POP) will have run out and another contraceptive started) for a short (10 min) telephone interview to determine contraceptive use, if they attended a GP or SRH service for this, if they used the POP (intervention arm only) and pregnancy status. If pregnancy has occurred then the validated London Measure of Unintended Pregnancy tool will be administered (18). If participants prefer, the questions can be self-completed by a survey emailed or sent to their mobile phone or by post. Research nurses will use local SRH data to validate whether participants attended the local SRH service, and which method of contraception they received. Women will receive a further interview (telephone call) from a research nurse at 12 months after recruitment, for a similar interview as at 4 months. If participants prefer, the questions can be self-completed by a survey emailed or sent to their mobile phone or by post.

With consent from participating women (agree to GP contact at recruitment), 5 % of participant's GP's will be contacted at 12 months to validate subjects reported contraceptive use. Information Services Division (ISD Scotland) and Department of Health (DOH England) will be given details of study participants and asked to determine the number of abortions occurring during the 12 month follow up period. ISD Scotland and the DOH England have both indicated support for this project and agreed to support linkage of the identifiers from study participants with abortion data registries (subject to necessary permissions).

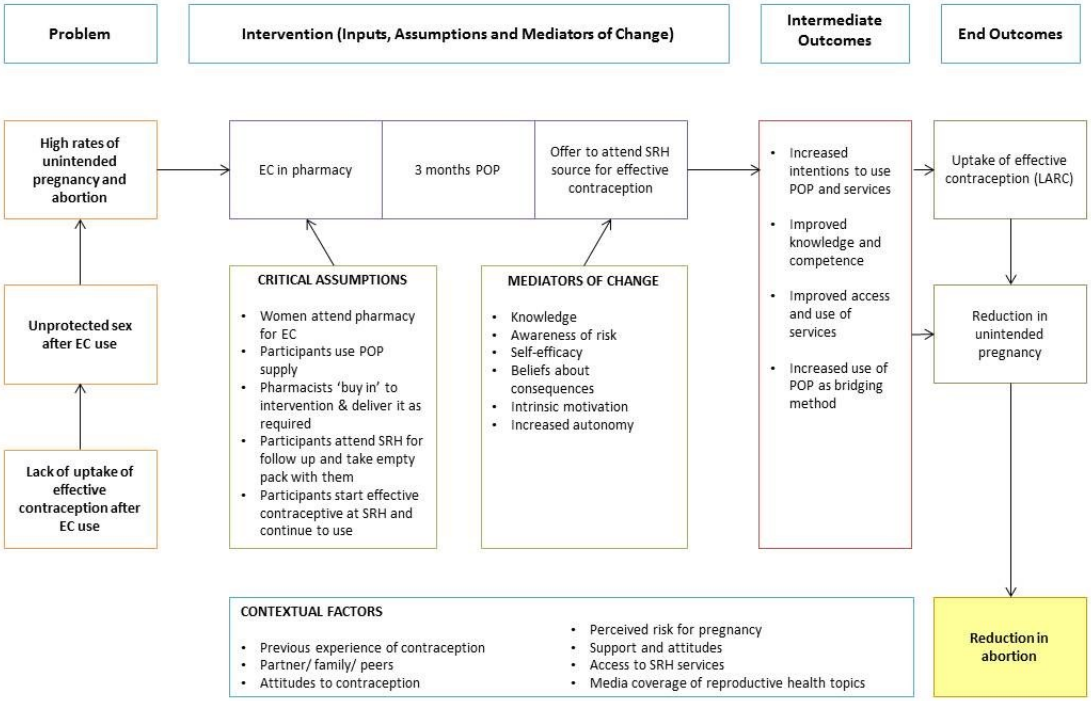
3.4 Design and theoretical/conceptual framework

Since further sex in the same cycle after taking EC increases the risk of an unintended pregnancy threefold, this underlines the importance of starting effective contraception immediately (10). Studies from Scotland and England have shown that when women access EC from a specialist contraceptive setting of a SRH service 24 to 50% of them will leave with an effective method of contraception (19, 20). However, the majority of women now choose to access EC from the community pharmacy (7) and pharmacists can usually only provide condoms (method of low effectiveness).

The formative research that we conducted for this proposal amongst women requesting EC from the community pharmacy in Scotland, showed that three quarters of women requesting EC had used a condom or no method and almost one half indicated that they would like to start an effective method demonstrating the opportunity for an intervention in the pharmacy to improve uptake of contraception (21). This study, together with the qualitative research of women in our pilot study, showed that women perceived that difficulty getting an appointment wither their GP as a factor that impacted upon non -use of effective contraception after EC (17,21). Women generally considered that a temporary supply of POP along with EC would be a good idea; giving them time to sort out ongoing contraception (17,21).

In addition, in a survey that we conducted of UK SRH clinicians who were attending a conference of the Faculty of Sexual and Reproductive Healthcare (90% doctors), 92% of were in favour of pharmacists being able to supply a temporary supply of POP along with EC, thus

providing women with temporary contraception until they can get an appointment with a contraceptive provider (21). The conceptual framework that forms the basis of this study is that at EC presentation, women will be motivated by this 'bridging POP plus invitation to SRH service ' intervention to commence effective contraception. If they commence LARC methods, then this should be associated with fewer unintended pregnancies (and reduced abortion rates) in the intervention cohort, since LARC methods have been shown to be most effective at preventing unintended pregnancy (11,22) (See figure below)



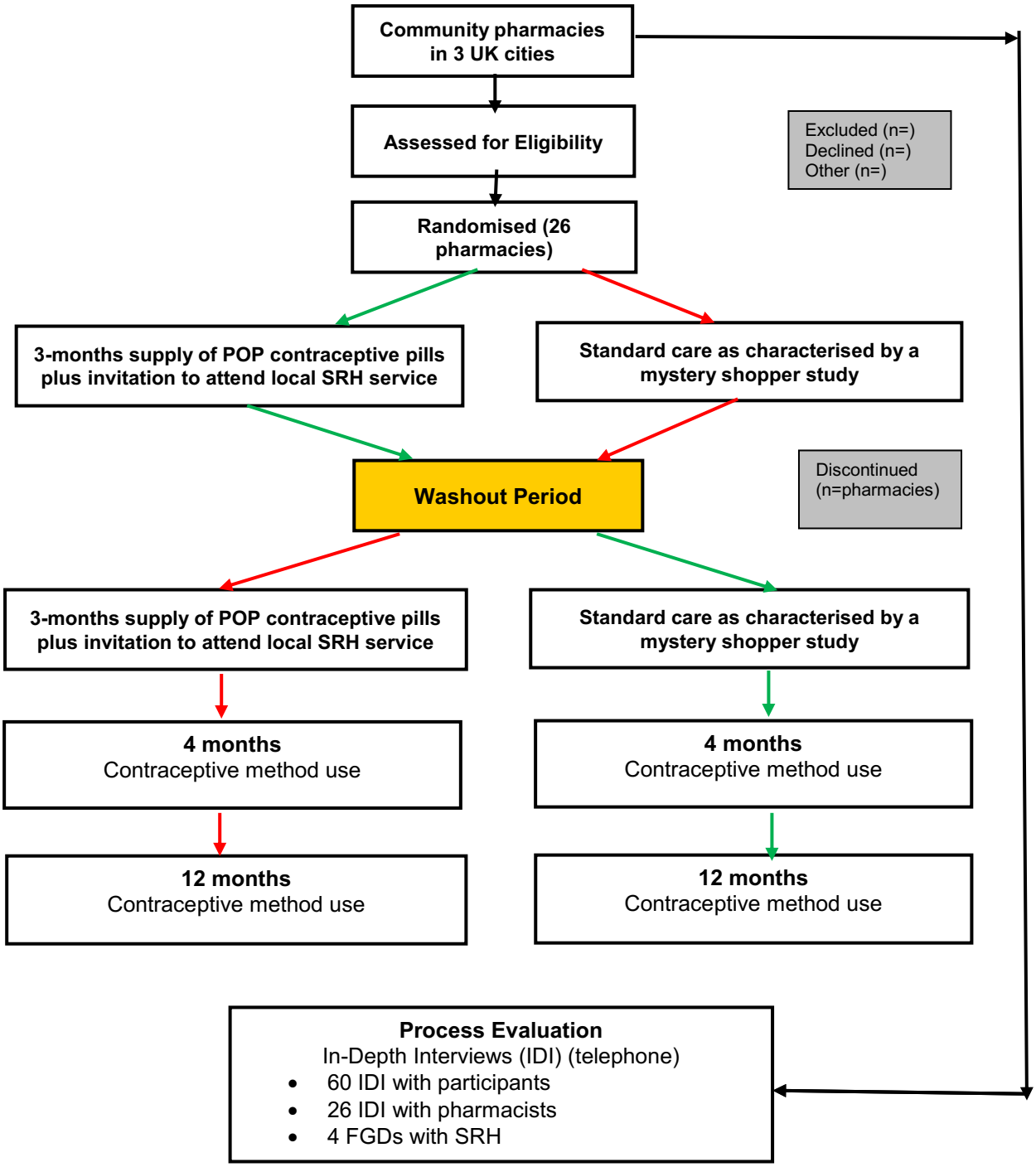
3.5 Target Population

Women (≥ 16 years) presenting to a participating community pharmacy requesting, and eligible for EC over the study recruitment period are potentially eligible for the study. We will exclude under 16 year olds since the age of consent to sex in the UK is 16 and 'underage' girls present certain management problems for pharmacists. Young women presenting for EC in UK pharmacies are routinely asked their age since those who admit to being under 16 are managed differently.

We plan to exclude women already using effective contraception (e.g. who have missed pills) as they would be advised to continue with the method rather than starting a bridging POP (10). Only women receiving oral EC Levonorgestrel (LNG) and in the standard dose (1.5 MG) will be eligible. Use of oral EC Ulipristal is currently uncommon in the UK and there are theoretical concerns regarding potential interactions with a POP that may reduce the efficacy of EC (23,24). The Faculty of Sexual and Reproductive Healthcare advises that women should not start a hormonal method of contraception for at least 5 days after Ulipristal (25).

The pharmacist will assess medical eligibility of women presenting, provide EC according to normal practice and invite eligible women to participate. Women who give written consent will be recruited in the study. We recognise the importance of participant retention and will offer a reward voucher at recruitment (26).

BRIDGE-IT Study Flowchart



4 STUDY POPULATION

4.1 Number of Participants

A total of 2080 women presenting for EC (1040 to standard care and 1040 to intervention

4.1.1 Inclusion Criteria

- Intake of EC (1.5 mg LNG)

- Capacity to give informed consent to participate in the trial which includes adherence to trial requirements
- Age 16 years or over
- Willing to give contact details and be contacted at 4 and 12 months by phone or text or e-mail or post.
- Willing to give identifying data sufficient to allow data linkage with NHS registries.

4.1.2 Exclusion Criteria

- Not willing to provide contact details or personal data sufficient to allow identification / linkage with NHS registries
- Contraindications to the POP e.g.
    - Active Venous thromboembolic disorder
    - Presence or history of severe hepatic disease
    - Undiagnosed vaginal bleeding
    - Hypersensitivity to the active substance
- On medication that interacts adversely with POP e.g.
    - Carbamazepine
    - Phenytoin
    - Rifampicin
    - Topiramate
    - St Johns Wart
- Age under 16
- Already using a hormonal method of contraception
- Require interpreting services
- If pharmacist has concerns about non-consensual sex

4.2 Co-Enrolment

Bridge-It is a pragmatic study. Women who are participating in other studies including trials of investigational medicinal products will be permitted to enter the study. The only exception would be if they were taking a drug at recruitment that interfered with either use of the LNG EC (i.e. fulfil inclusion/ exclusion criteria).

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 Identifying Participants

Women will be recruited from community pharmacies. This will be a mixture of pharmacies from a large UK chain (Boots UK) and independent pharmacies. All participating pharmacies have high rates of dispensing EC.

In our pilot study, large pharmacies performed much better than small ones where holidays, shifts, meal breaks and sickness absence interfered with recruitment. Enthusiasm waned with time. No pharmacy collected robust information on women declining to participate. We recognize the importance of motivating pharmacists to recruit actively and to collect robust data, therefore in our proposed trial a total of 26 pharmacies will allow a short recruitment period during which motivation can be sustained and performance monitored and fed-back.

We have support from the largest UK community pharmacy chain (Boots UK) who have confirmed that they will prioritise this study for us in their community pharmacies that

participate. All pharmacies (both independent and Boots) agreeing to participate in our study have consultation rooms and are open on Sundays and some evenings. We will use community pharmacies that serve both urban populations (Edinburgh, London) and rural populations (some of our study pharmacies in Tayside serve a predominantly rural population). Inclusion of London pharmacies should provide a diverse ethnic mix of women. The inclusion of sites in England and Scotland will permit findings that can be extrapolated across these slightly different health care systems in the UK.

At each site we have teamed up with a local SRH service (Chalmers Centre, Margaret Pyke, Dundee Ninewells, Perth and Kings College) obtaining support from the service leads to facilitate the study.

5.2 Consenting Participants

A detailed Patient Information Sheet (PIS) will be provided to all women and informed consent will be obtained by participating community pharmacists. Site specific information will be provided for each participating pharmacy. The local PI or a member of the research team will deliver on-site training on obtaining informed consent for the study to local teams.

5.3 Screening for Eligibility

All women who present for EC during the study and who fulfil the inclusion and exclusion criteria (section 4.2 and 4.3) will be invited to participate. The flowchart for determining eligibility and the patient pathway in the pharmacy is shown in **Appendix 5**.

5.4 Ineligible and Non-recruited Participants

Pharmacists will be asked to keep a screening log (ineligible/ declined form) of the numbers of women who presented for EC during the study period, the numbers approached to participate and numbers and reasons of declines and ineligibles.

5.5 Randomisation

5.5.1 Randomisation Procedures

This is a cluster crossover design so (a) it is the pharmacy that is the unit of randomisation and (b) the 'crossover' means that we are just randomising the order that each pharmacy gives the intervention in. We will generate a confidential list made up of a random mix of permuted blocks of size 2, 4 and 6 (100 units) and then assign the order by looking it up on the confidential list as new pharmacies join.

5.5.2 Treatment Allocation

The study is open i.e. women and pharmacy staff will know if they are receiving/providing the intervention

5.5.3 Emergency Unblinding Procedures

This is an open study and emergency unblinding is not required.

5.5.4 Withdrawal of Participants

Women may withdraw at any time without giving any reason and without affecting their clinical care in any way. A change of status form should be completed if this occurs. If a participant fails to respond to three message of contact (phone/ email/ post) at a single

timepoint, there will be no further contact at that time point. The participant will still be followed up at the next time point.

6. INTERVENTION

6.1 Emergency Contraception and Progesterone Only Pill

Women receive LNG EC as per routine care. Women in the intervention arm receive a composite intervention of a supply of POP and the offer of rapid access to a SRH service for ongoing contraception. The POP used in the study contains 75 mcg desogestrel. It will be provided to participants in the intervention arm according to a Patient Group Direction (PGD). It is routine stock, not labelled as a study drug.

6.2 Study Drug Manufacturer

The POP used in the study will contain 75 mcg desogestrel. This is currently available In the UK in both branded and generic formulations cerazette® (Schering) and cerelle ® (Gedeon Richter). Other brands in routine use can be used.

6.3 Dosing Regime

Women will receive LNG EC (1.5 MG) at the pharmacy to take as soon as possible. Women in the intervention phase will also receive one pack (3 months' supply) of POP (75 mcg desogestrel) with instructions to start this the next day and continue to take daily according to instructions. Participants may choose not to start the POP or to discontinue it when they wish.

6.4 Participant Compliance

Participants are women who present to the pharmacy for LNG-EC. They do not need to ingest this in the presence of a pharmacist. Use of the EC and the POP (intervention arm) will be determined from self -reports of women at telephone interview at 4 months post recruitment.

6.5 Overdose

The supply of the POP contains a patient information leaflet (PIL) on correct use of the POP and what to do if an overdose is taken. Overdosing of the POP is unlikely to cause serious adverse effects.

6.6 Other Medications

6.6.1 Contraindications

Women with contraindications to the POP or using enzyme inducing medications that may affect efficacy of the POP will not be recruited.

7. STUDY ASSESSMENTS

7.1 Study Assessments

Participant flow

Participant flow through the study will be assessed and reported following the CONSORT flow chart).

Participant demographics

Baseline demographics (collected at recruitment) will be reported.

Contraceptive use at 4 and 12 months

This will be based upon self -reported data from women at follow up interviews/ questionnaires. We will validate this for 5% of subjects by contacting GPs (of women giving permission for this).

Abortion rates at 12 months

The national registries (ISD and DOH) will be provided with details of participants and asked to provide data on the number of participants, and numbers of abortions in standard care and intervention groups who have had an abortion, and number by 1 year.

Process Evaluation

A process evaluation will be conducted as part of the study to assess potential issues concerning intervention implementation, the causal mechanisms of impact, and the contextual factors that could affect these. The process evaluation will comprise of quantitative and qualitative data collection, including: review of training and observation materials; observation of training; protocol adherence checklists and recruitment and monitoring forms (to be completed by pharmacists); semi-structured telephone interviews with participants (n=60), pharmacists (n=26), and SRH service providers (n=12); audit of local contraceptive services within 10 miles of study sites in London, Edinburgh and Dundee; and monitoring of contemporaneous events, such as relevant high coverage media stories using Google Alerts. See **Appendix 5** for process evaluation protocol.

Process Evaluation Analysis

All process data will be analysed independently of the outcome data and, importantly, documented before the outcomes are known. We will examine whether the theoretical constructs about how the intervention will work are supported or refuted by the data, with an eye to the unanticipated consequences of the intervention. As each stage of the study is completed, we will produce descriptive accounts of the data (e.g. audit; training observations; pharmacist and SRH provider interviews; participant questionnaires and interviews).

Quantitative analysis: data from screening logs etc. will be entered into SPSS for descriptive statistical analysis.

Qualitative analysis: In depth interviews will be recorded and transcribed verbatim. Transcription and analysis (proceeding case by case) will start with the first interview and be ongoing during the course of data collection, allowing for emergent themes to be identified and explored in future interviews. The transcripts will be read repeatedly and coded for analysis by the process evaluation research assistant (Susan Martin) , with the involvement of the Co-Investigator McDaid, to help prepare and agree a coding frame that will be used to code and chart the data. Data management will be assisted by ethnographic software, QSR NVivo 10. Analysis will be undertaken using 'Framework Analysis' a method of proven validity and reliability where data are coded, indexed and charted systematically, then organised using

a matrix or framework. Constant comparison will be carried out to ensure that the analysis represents all perspectives and negative ('deviant') cases.

The multi-source process evaluation will be synthesised to address the three key process evaluation questions: i) what was delivered, Iii) how it was delivered, and iii) what role context may have had in shaping the delivery/outcomes.

Cost Effectiveness Analysis

An economic evaluation will be undertaken comparing the intervention and control arms in a cost effectiveness analysis. A trial-based analysis will be followed by the construction of a decision model to extrapolate future costs and benefits beyond the completion of the trial. The overall perspective used will be that of the health system. Costs will include the pharmacist training to provide POP, direct and indirect costs of health service use, and the provision and dispensing of POP. We will compare the costs to the NHS in the intervention and control (standard access) arms. To account for differences in the numbers of women in the two arms, we will compare the cost per woman in each arm.

In the control arm, the costs are:

1. The cost of the LNG EC
2. The cost of pharmacist provision of EC
3. The cost of abortions

In the intervention arm, the costs are:

1. The cost of the LNG EC
2. The cost of pharmacist provision of EC
3. The cost of abortions
4. The cost of three packets of desogestrel POP.
5. The cost of pharmacist training to provide a three-month supply of desogestrel POP
6. The cost of pharmacist provision of desogestrel POP.

Since we will subtract the cost per women in the intervention arm from the cost per woman in the control arm, we can ignore the cost of 1 and 2 since they are the same in each arm. Therefore the (extra) cost of the intervention itself is the sum of 4, 5, and 6. The cost per women who has an abortion is the same in the two arms but we hypothesize that the abortion rate will be lower in the intervention group. We can then state the outcome as a conventional incremental cost-effectiveness ratio: every £100 spent on the intervention resulted in X fewer abortions for a savings of £Y. If Y is greater than 100 then the intervention is cost effective. We will examine the sensitivity of the outcomes to variations in the costs of 4, 5, and 6.

8. DATA COLLECTION

We will collect both quantitative and qualitative data.

Community pharmacists will keep screening logs (of women approached, eligible, declined) over the study period. Basic demographic details and reproductive history will also be collected from women who agree to participate (self-completed proforma).This information, together with consent forms from participants, will be entered directly to the secure study database (if electronic form). All study data that is collected in the pharmacies on paper forms will be anonymised (i.e stored with a study number only) and will be kept securely in a locked

cabinet. The contact information will be stored securely in the pharmacy and separated from the study data. This is in order to maintain confidentiality of all study participants. If electronic capture is not possible at the time, data will be collected on paper forms and stored securely until it is collected by a local study research nurse who will then enter the data onto the electronic study database that is password protected.

Research nurses will perform the 4 and 12 month follow up telephone interviews. This will be a 10 minute nurse administered telephone survey. If women prefer then this may be a self-completed survey completed (web based) or by post and sent by the Trial Office in Edinburgh. The interview/survey asks questions such as (if in intervention arm) did they use POP (and for how long), any side-effects, did they attend SRH or GP for contraception (if so when, what contraceptive method used, have they had repeat use of EC since recruitment, did pharmacist advise on ongoing contraception (if in control arm), and any pregnancies since recruitment (and if so then administration of the London Measure of Unintended Pregnancy (18)*)*. Information from the survey at 4 and 12 months will be entered onto the electronic study database by a member of the research team. Paper copies of the survey will be stored securely at the site where the data was collected.

Data will be collected on participants (in both study arms) who attended the SRH site during follow up for contraception. In Scottish sites this will be collected by the research nurse using the existing national sexual health database (NASH) employed by all SRH services. At London sites, the research nurses will collect this data from their local SRH databases.
Process evaluation interviews will be conducted and analysed by a study Research Assistant.
We will request ISD Scotland and DOH England to conduct linkage of participants (using provided identifiers) to abortion registries.

8.1 Data Processing

Data will be collected either on a paper case report form or will be entered directly into the trial database. Data will be entered into a trial database by pharmacists, research nurses or staff at the trial co-ordinating centre.

9. STATISCTICS AND DATA ANALYSIS

9.4 Sample Size Calculation

This cluster crossover study will have 90% power at a notional 5% level of significance (calculated at a 2.5% level to allow for the two primary outcomes of effective contraception at 4 months (Yes/No) and abortion within 12 months (Yes/No) with 26 pharmacies (clusters, calculated at 24 clusters to allow 2 clusters to be missing) with on average 30 evaluable women in each period (recruiting 40 to allow 25% loss to follow up in the patient reported outcome of effective contraception at 4 months) to detect increase in the proportion of those using effective contraception at 4 months of around 50% to 70%, depending on the underlying proportion in the control group. So for example if the control proportion is 20% using effective contraception at 4 months, the study would be highly powered to detect an improvement of 14% to 34% (relative risk 1.70). If the underlying rate was 30%, the study would be powered to detect an increase of 15% (to 45%, or a relative risk of 1.50). In our pilot study we saw control and intervention rates of 16% and 51%, although this was on a limited sample size in from one region. For the rarer outcome of having an abortion within 12 months, the control group will probably have around a 6-8% incidence. The study will have around 85% power at a nominal 5% level (calculated at 2.5%) of significance to detect a reduction to around 4.0 (a

relative risk of 0.5, assuming very little loss to follow up in this record linkage based outcome). Such a reduction is quite feasible given the increase in effective contraception, in particular LARC (which may improve from around 5% to over 10%). We would expect an increase in power by adjusting for any individual level covariates that were strongly predictive of outcome. Sample size calculations by simulation in R 3.0.3 for Windows using power.sim.binomial() within procedure 'clusterPower'. To be conservative we assumed a large between-cluster variance of 0.05 and a random effects analysis model, with 500 simulations performed.

9.5 Proposed Analyses

There will be a single analysis at study end (there is no opportunity for any interim analyses given the crossover design, although an independent Data Monitoring Committee (DMC) will monitor study progress and in particular any safety issues). This will follow the intention to treat principle, and use a hierarchical model appropriate for the specific outcome. So for the primary outcome this will be a mixed effects logistic regression, using the hierarchical model approach as recommended by Turner for a cluster crossover design (28). We will pre-specify any individual level (or cluster level) covariates that we intend to adjust for, and the comprehensive Statistical Analysis Plan will specify the sensitivity type analyses that will explore how robust the findings are to any missing data at the cluster level (probably unlikely) and the individual level (expected to be substantial for the patient reported outcomes at 4 and 12 months). As well as the usual assumption of missing at random, we will try to explore possible mechanisms for non-ignorable (informative missingness) at the individual level which may well be operating in this context.

10. SAFETY

The Bridge-It trial involves procedures and medications which are well established in current NHS clinical practice and use. Adverse events may occur during or after the use of medications and are well documented in the POP patient information leaflet. Adverse events will not be collected during this trial. We will only collect serious adverse events reported at the 4 month follow up interview, following the trial intervention phase. The local PI or their delegate at the site will categorise these as expected or unexpected.

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

10.1 Definitions

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

Adverse events are not:

- Continuous and persistent disease or symptom, present before the trial, which fails to progress.
- Treatment failure.

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant 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.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) or Investigators Brochure.

10.2 Expected Adverse Events

In this study the following events are potentially expected and will not be collected:

Levonelle (Levonorgestrel)

Very Common (≥10%)
Headache
Nausea
Lower abdominal pain
Bleeding not related to menses (Bleeding patterns may be temporarily disturbed, but most women will have their next menstrual period within 7 days of the expected time)
Fatigue

Common(≥1/100 to <1/10)
Dizziness
Diarrhoea
Vomiting
Delay of menses more than 7 days
Irregular menstruation
Breast tenderness

Cerazette (Desogestrel)

Common
Mood altered, Depressed mood, libido decreased
Headache
Nausea
Acne
Breast pain, Menstruation irregular, amenorrhoea

Uncommon
Vaginal infection
Contact lens intolerance
Vomiting
Alopecia

Dysmenorrhoea, ovarian cyst
Fatigue

10.3 Identifying AEs and SAEs

Only serious events related to the intervention will be recorded on the SAE form. Planned primary care or hospital visits for conditions other than those associated with the study will not be collected or reported. SAEs will be recorded from the time a participant signs the consent form until the 4 month interview.

Participants will be asked at the interview if they had any hospital admissions in the last 4 months since participating in the Bridge-it study. If the answer to the question is yes, the research nurse will collect further details by phone

Recording AEs and SAEs

When an SAE occurs, it is the responsibility of the Investigator to review any documentation available related to the event. The Investigator/Research Nurse will then record all relevant information on the SAE form.

Information to be collected includes type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.4 Assessment of SAEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator or delegated individual.

The Investigator is responsible for assessing each SAE.

The Investigator will make an assessment of seriousness as defined in Section 10.1.

10.5 Assessment of Causality

The Investigator will make an assessment of whether the SAE is likely to be related to the trial according to the definitions below.

- Unrelated: where an event is not considered to be related to any of the trial procedures
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the SAE has a causal relationship to the study procedures. The assessment of causality will be made against the reference safety information found in the reference safety information of the SmPC.
-

Alternative causes such as concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

10.6 Assessment of Expectedness

When assessing expectedness refer to the expected events (section 10.2)and SmPC.

10.7 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.8 Reporting of SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.5.2, Assessment of Causality and 10.5.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

10.9 Reporting Requirements

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the relevant ethics committee (Research Ethics Committee (REC) that approved the trial Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information

10.10 Follow-up Procedures

After reporting an SAE, the Investigator will follow each participant until resolution or death of the participant. Follow up information on an SAE will be reported to the ACCORD office.

11. PREGNANCY

Pregnancy is not considered an AE or SAE; however, the research nurses will collect pregnancy information for the participants at the 4 and 12 month follow up interviews.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 Trial Management Group

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh and Co-Investigators), a Trial Manager and coordinating nurse and the process evaluation Research Assistant.

The Trial Manager at Edinburgh University will oversee the study and will be accountable to the Chief Investigator. A trial manager at the Centre for healthcare Randomised Trials (CHaRT) at Aberdeen University will provide some management support. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial. . A Decision Log will be prepared to record all decisions pertaining to the management of the trial.

12.2 Trial Steering Committee

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The membership of this committee is comprised of three independent members along with the Chief Investigator or a nominated delegate. The trial sponsor, other Bridge-It grant-holders and key members of the central office (e.g. the trial manager) can participate in TSC meetings but are not members. The funder will be notified in advance of meetings and a representative invited to attend. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in Appendix 2. The TSC will meet approximately yearly.

12.3 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The DMC will be made up of three members, one of whom is an experienced statistician. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in Appendix 2.

The Committee will meet regularly to monitor the data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

12.4 Inspection of Records

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 Risk Assessment

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance (QA) Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

12.6 Study Monitoring and Audit

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

13. GOOD CLINICAL PRACTICE

13.1 Ethical Conduct

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

Annual progress reports and a final report at the conclusion of the trial will be submitted to REC (insert ethics committee) within the timelines defined in the regulations.

13.2 Investigator Responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

13.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the clinic or hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

13.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

13.2.3 Investigator Documentation

The Principle Investigator, Research Nurse or designee is responsible for the quality of the data recorded in the CRF at each Investigator site and will ensure that the required documentation is available in the Local Investigator Site File (ISFs).

13.2.4 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated on their respective CVs.

13.2.5 Confidentiality

All evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.2.6 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities. The senior IT manager at CHaRT (in collaboration with the CI) will manage access rights to the data set. Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14. STUDY CONDUCT RESPONSIBILITIES

14.1 Protocol Amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

14.2 Protocol Deviations and Violations

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 24 hours of becoming aware of the violation.

14.3 Serious Breach Requirements

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.4 Study Record Retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.5 End of Study

The end of study is defined as the last participant's last visit.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC within 1 year of the end of the study. An end of trial report is also required by the NIHR HTA at the end of funding.

14.6 Insurance and Indemnity

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 Authorship Policy

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

15.3 Peer Review

The protocol has been reviewed by the Bridge –IT investigators and Chart.

16. REFERENCES

1. Sedgh G, Singh S, Shah IH, Ahman E, Henshaw SK, Bankole A. Induced abortion: incidence and trends worldwide from 1995 to 2008. Lancet. 2012 Feb 18;379(9816):625-32.

2. Department of Health. Abortion Statistics, England and Wales: 2014. https://www.gov.uk/government/publications/report-on-abortion-statistics-in-england-and-wales-for-2014 (access date 11 Jan 2016)

3. Information Services Division. Abortion Statistics 2014 http://www.isdscotland.org/Health-Topics/Sexual-Health/Abortions/ (access date 11 Jan 2016)

4. Wellings K, Jones KG, Mercer CH et al The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). Lancet 2013;382:1807-16

5. Thomas C, Cameron ST. Can we reduce costs and prevent more unintended pregnancies? A cost of illness study illustrating the cost-saving potential of a more effective method of EHC. BMJ open 2013;3:e003815.doi:10.1136

6. SmithBattle L, Leonard V. Inequities compounded: explaining variations in the transition to adulthood for teen mothers' offspring. J Fam Nurs. 2012;18(3):409-31.

7.Marston C, Meltzer H, Majeed A. Impact on contraceptive practice of making emergency hormonal contraception available over the counter in Great Britain: repeated cross sectional surveys.BMJ. 2005 Jul 30;331(7511):271.

8. Polis CB, Grimes DA, Schaffer K, Blanchard K, Glasier A, Harper C. Advance provision of emergency contraception for pregnancy prevention. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005497. DOI:0.1002/14651858.CD005497.pub2.

9. Cheng L, Che Y, Gülmezoglu AM. Interventions for emergency contraception. *Cochrane Database of Systematic Reviews* 2012;Issue 8. Art. No.: CD001324. DOI: 10.1002/14651858.CD001324.pub4.

10. Faculty of Family Planning & Reproductive Healthcare Clinical Effectiveness Unit. Emergency Contraception Guidance. January 2012.http://www.fsrh.org (Access date 11 Jan 2016)

11.Glasier A, Manners RJ, Loudon JC, Muir A. Community pharmacists providing emergency contraception give little advice about future contraceptive use: a mystery shopper study. Contraception 2010;82: 538–42.

12. Michie L, Cameron ST, Glasier A et al .Pharmacy based interventions for initiating effective contraception following the use of emergency contraception: a pilot study. Contraception 2014 ;90, 447-53

13.National Institute for Health and Clinical Excellence. Long-acting reversible contraception.http://www.nice.org.uk/nicemedia/live/10974/29912/29912.pdf (access date 1 Jan 2016)

14. Trussell J. Contraceptive efficacy. Glob Libr Womens Med [last accessed 06.05.14], ISSN: 1756-2228, http://dx.doi.org/10.3843/GLOWM10375. This chapter was last updated, http://www.glowm.com/section_view/item/374; 2014.

15. Bednarek PH, Creinin MD, Reeves MF, et al. Post-Aspiration IUD Randomization (PAIR) study trial group. Immediate versus delayed IUD insertion after uterine aspiration. N Engl J Med 2011;364:2208e17.

16. The Faculty of Sexual and Reproductive Healthcare (FSRH). UK medical Eligibility criteria for Contraceptive Use. http://www.fsrh.org/standards-and-guidance/uk-medical-eligibility-criteria-for-contraceptive-use/ (access date 6 Feb 2017)

17. Michie L, Cameron ST, Glasier A, Chen ZE , Milne D, Wilson S. Providing bridging contraception after emergency contraception from the pharmacy: a qualitative study. Public Health 2016 Jun;135:97-103.

18. Cameron ST ,Glasier A. Identifying women in need of further discussion about the decision to have an abortion and eventual outcome. Contraception. 2013**;** 88(1): 128-32

19. Cameron ST, Glasier A, Johnstone A, Rae L. Ongoing contraception after use of emergency contraception from a specialist contraceptive service. Contraception 2011; 84 (4) 368-371

20. Baird AS. Use of ulipristal acetate, levonorgestrel and the copper-intrauterine device for emergency contraception following the introduction of new FSRH guidelines.J Fam Plann Reprod Health Care. 2013 ;39(4):264-9

21. Michie L, Cameron ST, Glasier A, Greed E. Contraceptive use among women presenting to pharmacies for emergency contraception: an opportunity for intervention.J Fam Plann Reprod Health Care. 2014, 40(3):190-5

22. Piepert JF, Madden T, Allsworth JE, Secura GM. Preventing Unintended Pregnancies by Providing No-Cost Contraception. Obstet Gynecol 2012 ; 120:1291–7.

23**.** Cameron ST, Berger C, Michie L , Klipping C , Gemzell –Danielsson K. The effects on ovarian activity of 'quickstarting' a combined oral contraceptive pill after ulipristal acetate : prospective, randomised, double-blind parallel-arm, placebo-controlled study. Hum Reprod 2015;30(7):1566-72

24. Brache V, Cochon L, Duijkers IJ, Levy DP, Kapp N, Monteil C, Abitbol JL, Klipping C.A prospective, randomized, pharmacodynamic study of quick-starting a desogestrel progestin-only pill following **ulipristal** acetate for emergency contraception.Hum Reprod. 2015 ;30(12):2785-93.

25. Statement from the clinical effectiveness unit september 2015. http://www.fsrh.org/pdfs/CEUStatementQuickStartingAfterUPA.pdf (access date 11 Jan 2016)

26. Brueton VC, Tierney J, Stenning S, Harding S, Meredith S, Nazareth I, Rait G. Strategies to improve retention in randomised trials. Cochrane Database Syst Rev. 2013 Dec 3; 12:MR000032. doi: 10.1002/14651858.MR000032.pub2.

26. Ritchie J, Spencer L. Carrying out qualitative analysis. Qualitative research practice: a guide for social science students and researchers. Sage, London (2003)

27. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: new guidance. London: Medical Research Council. 2008

28. Turner RM, Omar RZ, Thompson SG. Modelling multivariate outcomes in hierarchical data, with application to cluster randomised trials. Biom J. 2006 Jun;48(3):333-45.

Appendix 1 – Trial Steering Committee

Prof Peter Brocklehurst (chair) TSC	Methodologist/Statistician/ Epidemiologist	P.Brocklehurst@bham.ac.uk
Dr Lucy Michie	Sexual and Reproductive health, Sandyford Glasgow,.	michieluc@yahoo.co.uk
Prof Kaye Wellings	LSHTM, Qualitative expertise, EC expertise	Kaye.wellings@lshtm.ac.uk
Emily Whittaker	PPI member	emily6ocdn@gmail.com
Joanna Loudon (PPI)	PPI member	Joanna.loudon@nhslothian.scot.nhs.uk
Kirsten Stuart (PPI)	PPI member (chair)	kirstenstuart@yahoo.co.uk

Appendix 2 – Data Monitoring Commitee

Prof Claire Anderson (Chair)	Pharmacy, Nottingham	Claire.Anderson@nottingham.ac.uk
Prof Caroline Moreau	Epidemiology, INSERM, John Hopkins	caroline.b.moreau@gmail.com
Prof Elizabeth Allen	Statistics, LSHTM	Elizabeth.Allen@lshtm.ac.uk

Appendix 3 – Mystery Shopper Exercise

We envisage that 2 individuals would be necessary for the mystery shopper exercise at each site.

Example scenario :
eg. requesting EC for unprotected intercourse which (if asked) had occurred the night before, with no other acts of intercourse in that cycle and the last (normal) menstrual period starting 11 days earlier.

Data collection proforma
A tick box proforma (with space for free text) will be used based on the following elements:

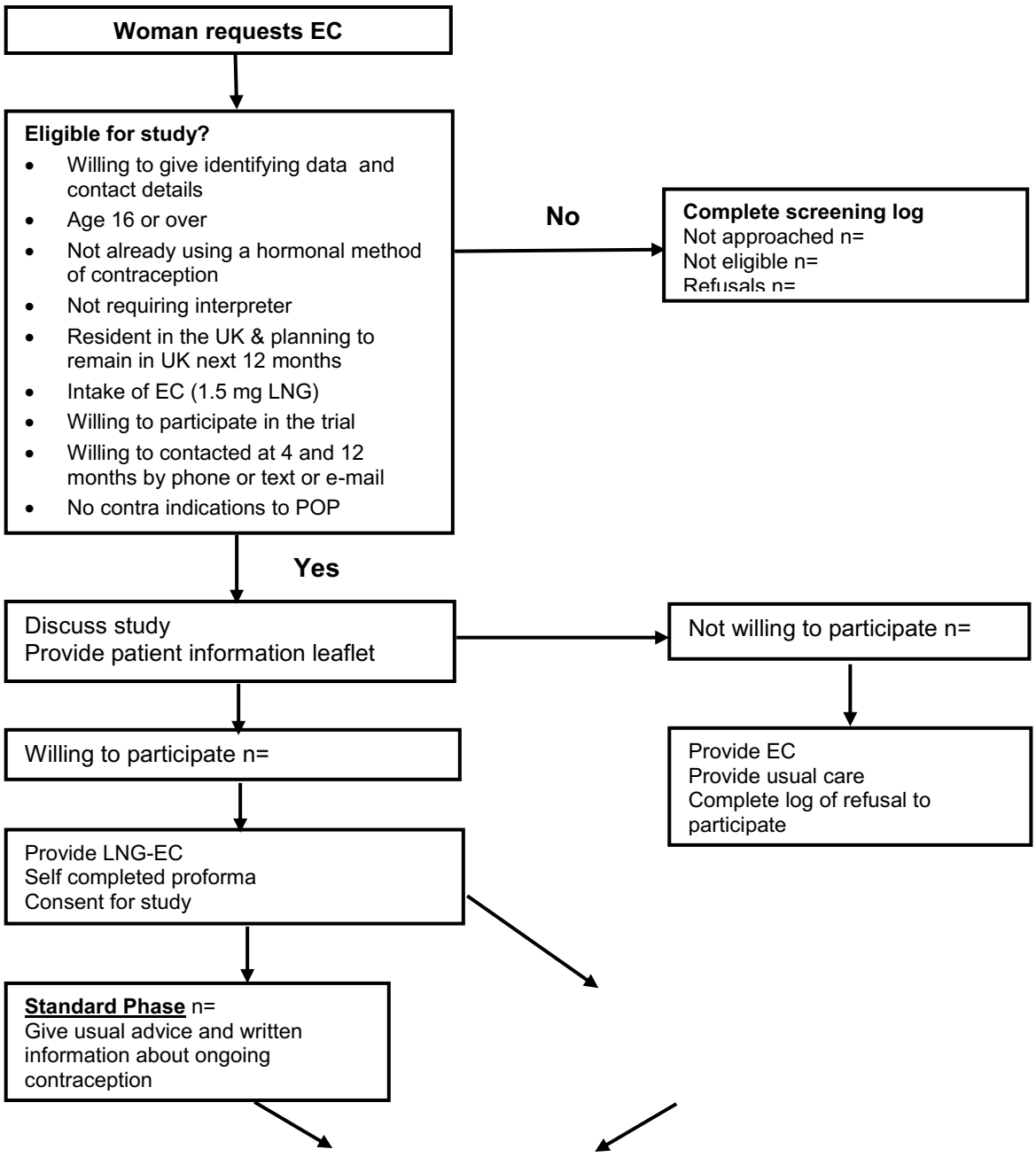
Pharmacy Name / address:
Date:
Tick if the following were covered during the consultation:

- Reason for needing, or eligibility for EC
- Verbal information/advice about importance of contraception after EC
- **Written** information/advice about importance of contraception after EC
- Verbal Information about local SRH clinic/ GP for contraception
- **Written** information/advice about importance of contraception after EC

- Verbal information/advice about pregnancy test in 3 weeks
- **Written** information/advice about pregnancy test in 3 weeks

- Consultation took place: private room/ at counter/ other
- Duration:
  Time entering pharmacy
  Time of start of consult with pharmacist
  Time of end of consult with pharmacist

Appendix 4 – Pharmacy Pathway Flowchart



Appendix 5 – The 'Bridge-It' Study Process Evaluation Protocol

Lisa M McDaid – Process Evaluation Lead
Susan Martin – Process Evaluation Research Assistant

1 Background and Rationale

A process evaluation will be conducted as part of the 'Bridge-it' study as it is essential to properly understand potential issues concerning intervention implementation, the causal mechanisms of impact, and the contextual factors that could affect these. We include process evaluation in this trial in order to understand why this trial works (or not) for whom, and why.

The Bridge-it process evaluation is led by Dr Lisa McDaid and supported by a 0.75FTE Research Assistant at MRC/CSO SPHSU (Susan Martin).

2 Aims

To assess intervention implementation, fidelity and reach to contribute to evaluating the effectiveness of the intervention, by assessing what was delivered, how it was delivered, and what role context may have had in shaping the delivery/outcomes to inform future roll out/implementation. Specifically, the process evaluation will assess:

- **Implementation**: implementation process (*how* delivery was achieved, i.e., training);
- **Fidelity**: *what* was delivered (i.e., adherence to training protocol, dose and duration of intervention), adaptations and reach, by study site; *what* was received by participants;
- **Participation and reach**: uptake of the intervention by providers (pharmacists, SRH service providers) and participants;
- **Reception and responsiveness**: acceptability of the intervention to providers (pharmacists, SRH service providers) and participants;
- **Context**: local context of the intervention, as relevant to its implementation / mechanisms of change / outcomes (e.g., barriers/facilitators to implementation); broader context in which the trial/intervention has taken place (e.g., local/national policies and action which may impact the intervention).

Collection of these data allows us to assess the role of our critical assumptions, mediators of change, and intermediate outcomes (see logic model) that could impact on the effectiveness of the intervention.

3 Methods

The Process Evaluation requires quantitative data on recruitment, participation and reach and detailed qualitative data from those delivering the trial (community pharmacists/SRH service providers) and those receiving it (women).

3.1 Overview of the methods for process evaluation

Theory
Theory of change model
Study Team
Pharmacy recruitment forms (completed by study team members involved in recruitment)
Pharmacists
Participant observation of training & review of training and intervention materials Recruitment monitoring forms (n=100% of pharmacists) & protocol adherence checklists (n=100% of pharmacists) Follow-up semi-structured telephone interviews with pharmacists (n=26; one with each pharmacy involved).
SRH Providers
Participant observation of training & review of training and intervention materials Recruitment monitoring forms (n=100% of providers) & protocol adherence checklists (n=100% of providers) Semi-structured telephone interviews with SRH providers (n=12; with Service Manager, mix staff at 2x services in London; 1x service in Edinburgh; 1x service in Dundee).
Participants
Telephone questionnaire administered by Research Nurse at 4 months post-intervention (n=100% participants) Telephone questionnaire administered by Research Nurse at 12 months post-intervention (n=100% participants) Semi-structured telephone interviews at 4 months post-intervention (n=60; 34 in London, 18 in Edinburgh and 8 in Dundee)
Context
Audit of local contraceptive services within 10 miles of study sites in London, Edinburgh and Dundee Monitoring of contemporaneous events, such as relevant high coverage media stories using Google Alerts

3.2 Study Team and Recruitment

To assess participation and reach, recruitment of pharmacists will be monitored using a standardised template format. Study team members who are recruiting pharmacists will routinely record decision making contributing to pharmacy selection, including: number of contacts made; responses from potential pharmacists; rationales for inclusion/exclusion; and reasons for refusal.

3.3 Pharmacists

Pharmacists recruited to deliver the intervention will undertake training and be provided with a study protocol and detailed manual. Training sessions for pharmacists will be observed by the process evaluation Research Assistant and all intervention and training materials will be reviewed. Particular attention will be paid in training to the way key mechanisms of the intervention are presented to, and understood by, pharmacists. Key details will be recorded on an observation form and in fieldnotes.

To assess implementation, fidelity, participation and reach, recruitment monitoring forms will be completed by all pharmacists trained to deliver the intervention, using a standardised template format. Protocol adherence checklists will be completed by all pharmacists for all participants recruited into the trial.

Follow-up semi-structured telephone interviews will be conducted with a sample of pharmacists (n=26, one from each pharmacy involved). These interviews will explore pharmacists' perceptions of barriers and facilitators to implementation and more broadly, their views on the intervention, the trial, and the target population. Interviews will be conducted by the process evaluation research assistant soon after the intervention phase has completed, and will focus on:

- clarity, consistency and quality of training and intervention materials
- perceived work required to deliver the intervention/trial
- confidence/consistency in delivering the intervention and adhering to the protocol/training manual
- acceptability of the intervention
- experiences of delivering the intervention and challenges faced
- perceived barriers to women's participation in the trial
- suggested changes to the intervention if it were to be more widely implemented
- pharmacists' decision-making, and their perceptions of women requesting EC
- pharmacists' professional backgrounds, and previous training in similar interventions

3.4 SRH Providers

Semi-structured telephone interviews will be conducted with a sample of SRH providers (n=12; with Service Manager, mix staff at 2x services in London, 1x service in Edinburgh; 1x service in Dundee) to explore their perceptions of barriers and facilitators to intervention

implementation and more broadly, their views on the trial, and the target population. These interviews will be conducted by the process evaluation research assistant soon after the intervention phase has completed.
They will focus on the quality and quantity of what was implemented, together with the practicalities and barriers of delivering the intervention. Interviews will explore:

- clarity, consistency and quality of training and intervention materials
- perceived work required to deliver the intervention/trial
- confidence/consistency in delivering the intervention and adhering to the protocol/training manual
- acceptability of the intervention
- experiences of delivering the intervention and challenges faced
- perceived barriers to women's participation in the trial
- suggested changes to the intervention if it were to be more widely implemented
- SRH providers' decision-making, and their perceptions of women requesting EC
- SRH providers' professional backgrounds, and previous training in similar interventions [collected quantitatively at the start of the focus group]

3.5 Participants

Telephone questionnaires will be administered by Research Nurses at 4 months post-intervention to all participants. For the process evaluation, the questionnaires will collect data on aspects of fidelity, reception and responsiveness, context, including:

- participant characteristics (e.g. partner relationships)
- experience of contraception
- reasons for attending for emergency contraception (EC)
- nature of service received in the pharmacy (tailored to control/intervention arm)
- participation in the intervention (ie, if used EC/POP, accessed SRH service, started effective contraception, and if not, why not)
- delivery of key mechanisms by SRH Providers
- acceptability of the intervention

Telephone questionnaires will be administered by Research Nurses at 12 months post-intervention to all participants. For the process evaluation, the questionnaires will collect data on aspects of context, including:

- changes in circumstances (e.g., change of partner) that could affect contraceptive use
- continued effective contraception, and if not, why not

Recruitment and retention rates of participants should be monitored via the telephone interviews and Research Nurses will record the number and outcomes of call attempts made; as well as the number and reason (if provided) for withdrawal from the study.

Post-trial quantitative analyses will use the data on participant characteristics to investigate which participants benefited most from the interventions.

Semi-structured, qualitative telephone interviews of a purposive sample[1] of 60 women who received the intervention (34 in London, 18 in Edinburgh and 8 in Dundee) will be undertaken for a qualitative interview at the end of the 4 months questionnaire. Interviews will explore experience of issues of intervention acceptability in more depth and qualitative assessment of their experiences of bridging from EC to regular contraception, and reasons for doing so/ not choosing to do so. Interviews will be conducted soon after the 4 months follow up and within 6 months of enrolment into the trial. The interviews will assess fidelity, reach, reception and responsiveness and context. The topic guide will include:

- understanding of the trial
- experiences of recruitment to trial
- understandings of, and responses to, key mechanisms
- reflections on experience of participating in the intervention [in pharmacy, using EC/POP, accessing SRH service]
- acceptability of the intervention
- whether the intervention prompted change and/or any negative or unintended consequences
- subsequent contraceptive use [depending on when interviews are]
- the wider context of their lives and experiences of using EC/contraception, including the circumstances surrounding request for EC at recruitment
- Relevant background information (e.g. relationship with partner; family; friends, and attitudes to/support for EC/contraceptive use, response to participation)

Unintended consequences will be documented through the process evaluation, including asking participants whether they perceived any unintended negative outcomes resulting from participating in the trial.

3.6 Context

We will audit and map contraceptive services/interventions that are available to women in the intervention cities to hypothesise on whether any changes observed could be the result of, or affected by, activities and services other than the intervention and whether there are particular features of the participating centres that could have affected outcomes. This will include a desk-based audit of the pharmacies/SRH services participating in the study, which will collect data on the size, location, accessibility, footfall, distribution of EC and other services provided by these. We will also audit other local contraceptive services and pharmacies within 10 miles of study sites in London, Edinburgh and Dundee to hypothesise on whether any changes observed could be the result of, or affected by, activities and

[1] The purposive sample will be based on a breakdown of groups that we hypothesise will experience the intervention differently (e.g., by age, socio-economic status, previous emergency contraception use etc).

services available elsewhere in the local environment. A short online mapping questionnaire will be developed and distributed to key stakeholders and organisations to collect brief details on: the nature of the activity/service provided by the organisations; where, how and by whom it is delivered; the target user group, capacity and uptake (if known); and how the service is linked to others. Reported activities and services will be checked for relevance by the process evaluation Research Assistant.

Finally, we will monitor local, national and international contemporaneous events that could impact on contraceptive use and behaviour over the course of the study, such as relevant high coverage media stories using Google Alerts and relevant search terms to hypothesise on potential confounding and contamination to the trial.

3.7 Analysis

All process data will be analysed independently of the outcome data and, importantly, documented before the outcomes are known. We will examine whether the theoretical constructs about how the intervention will work are supported or refuted by the data, with an eye to the unanticipated consequences of the intervention. As each stage of the study is completed, we will produce descriptive accounts of the data (e.g. audit; training observations; pharmacist and SRH provider interviews; participant questionnaires and interviews).

Quantitative analysis: data from screening logs etc will be entered into SPSS for descriptive statistical analysis.

Qualitative analysis: In depth interviews will be recorded and transcribed verbatim. Transcription and analysis (proceeding case by case) will start with the first interview and be ongoing during the course of data collection, allowing for emergent themes to be identified and explored in future interviews. The transcripts will be read repeatedly and coded for analysis by the research assistant (Susan Martin) employed on the study, with the involvement of the Co-Investigator McDaid, to help prepare and agree a coding frame that will be used to code and chart the data. Data management will be assisted by ethnographic software, QSR NVivo 10. Analysis will be undertaken using 'Framework Analysis' a method of proven validity and reliability where data are coded, indexed and charted systematically, then organised using a matrix or framework. Constant comparison will be carried out to ensure that the analysis represents all perspectives and negative ('deviant') cases.

The multi-source process evaluation will be synthesised to address the three key process evaluation questions: i) what was delivered, Iii) how it was delivered, and iii) what role context may have had in shaping the delivery/outcomes.