VARIATIONS IN THE ORGANISATION OF EARLY PREGNANCY ASSESSMENT UNITS (EPAUs) IN THE UK AND THEIR EFFECTS ON CLINICAL, SERVICE AND PATIENT-CENTRED OUTCOMES (STUDENT STUDY)

ORGANISATION OF EARLY PREGNANCY UNITS AND ITS EFFECT ON QUALITY OF CARE
VESPA STUDY

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PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	3.0	18/05/17	Maria Memtsa, Clinical Research Fellow	
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	1.1	28/06/16	Maria Memtsa, Clinical Research Fellow	
	1.0	23/06/16	Maria Memtsa, Clinical Research Fellow	

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:..... **.....**

Date..15..../..07..../...16....

Print Name(in full):.....Mr Davor Jurkovic.....

Position:.....Chief Investigator.....

On behalf of the Study Sponsor:

Signature:..  **..**

Date14./.JULY/.2016

Print Name(in full):...JENISE DAVIDSON.....

Position:..PORTFOLIO COORDINATOR

STUDY SUMMARY

Identifiers	
IRAS Number	179311
REC Reference No	16/NW/0587
Sponsor Reference No	16/0347
Other research reference number(s) (if applicable)	
Full (Scientific) title	Variations in the organisation of Early Pregnancy Assessment Units (EPAUs) in the UK and their effects on clinical, service and patient-centred outcomes
Health condition(s) or problem(s) studied	Early Pregnancy
Study Type i.e. Cohort etc	Multi-methods approach
Target sample size	6,800
STUDY TIMELINES	
Study Duration/length	24 months
Expected Start Date	01/11/15
End of Study definition and anticipated date	The end of the study will be defined as the last 26-week/3-month follow-up visit for a participating patient. The study will be considered closed when the last patient has reached this time-point, all data are complete and all data queries have been resolved. Anticipated end date: 31/10/17
Key Study milestones	First patient recruitment: 10/01/17
FUNDING & Other	
Funding	Health Services and Delivery Research Programme
KEY STUDY CONTACTS	
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KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the RE of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

STUDY MANAGER: Dr Maria Memtsa

CO-APPLICANTS:

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KEY WORDS

Early pregnancy units, organisation, outcomes

LIST OF ABBREVIATIONS

AEPU	Association of Early Pregnancy Units
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
EPAU	Early Pregnancy Assessment Unit
GAfREC	Governance Arrangement for NHS Research Ethics
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Studies Number
NICE	National Institute for Health and Care Excellence
PI	Principle Investigator
PIL	Participant Information Leaflet
RCOG	Royal College of Obstetricians & Gynaecologists
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics committee
SOP	Standard Operating Procedure
SSI	Site Specific Information
SMF	Study Master File
SSC	Study Steering Committee

CONTENTS

1 INTRODUCTION

A recent NICE guideline on "Ectopic pregnancy and miscarriage" (CG154)[1] published in December 2012 emphasises the need for good quality research to establish the effectiveness of Early Pregnancy Assessment Units (EPAUs). EPAUs are dedicated units within NHS hospitals that provide specialist care to women in the first three months of pregnancy. Women who experience pain or bleeding in the first weeks of pregnancy or women with a previous miscarriage or ectopic pregnancy are routinely seen in EPAUs. While most NHS hospitals in the UK have an EPAU, there are considerable variations between EPAUs in the levels of care they provide and their accessibility to women. In addition, staffing levels vary considerably between the units. The most cost-effective organisational model for an EPAU is unknown.

Early pregnancy problems are very common with 20% of recognised pregnancies ending in miscarriage and 2% of pregnancies being complicated by an ectopic pregnancy. Given the variation amongst units, women are likely to have different experiences of the services and the care provided.

We recently completed a pilot study of seven EPAUs across London to compare several clinical and service outcomes in units with different organisational structures, staffing levels and ease of access.

The study showed differences in several important clinical outcomes between different units. We used these findings to plan a larger study, which is described in this protocol.

We propose to collect information about all women who present to a sample of EPAUs, with suspected complications of early pregnancy, for initial or follow-up visits.

The main outcome of interest is the number of women who require emergency admission and stay in hospital. This could be either because a diagnosis cannot be made with certainty in the EPAU clinic, or because of the need for further treatment.

In addition to the primary outcome we will:

a) Examine the number of follow-up visits and ultrasound scans that are required to reach a diagnosis.
b) Look at the number of surgical keyhole procedures that were performed for suspected ectopic pregnancy and the number of procedures which did not confirm this diagnosis.
c) Record all women who had a burst ectopic pregnancy and required a blood transfusion.
d) Collect and analyse information about women's experiences of the care they received in an EPAU and their satisfaction with it.
e) Conduct workforce modelling of the most effective EPAU staffing configuration(s), based on the primary outcome.
f) Conduct a cost-effectiveness analysis of alternative workforce models.

We have estimated that we need to include 44 EPAUs nationwide. We based our calculations on our findings from the smaller study, which showed that quality of care appears to be better in the units where senior doctors (consultants) tend to spend more time working with other staff members who are looking after pregnant women. We will ensure that the units included in the study represent a good mixture of units located within both different types of hospitals and different geographic areas within the UK. The study will last for 2 years.

The research team includes clinicians, academics, and lay members, and the conduct of the study will be overseen by a Study Steering Committee. The information obtained from this study will help to better organise EPAUs nationwide in order to ensure optimal clinical outcomes in the most cost effective way.

2 BACKGROUND AND RATIONALE

There are currently an estimated 200 EPAUs in the UK in NHS hospitals[2], according to the Association of Early Pregnancy Units (AEPU). EPAUs provide clinical care and support to women presenting with pain and bleeding in the first trimester of pregnancy. The National Service Framework[3] recommends that EPAUs should be generally available and easily accessible, set up in a dedicated area in the hospital, with appropriate staffing and ultrasound equipment, as well as easy access to laboratory facilities. There should be direct referral access for GPs, and selected patient groups, such as women who experienced an ectopic or molar pregnancy in the past.

However, there is considerable variation between different units in the levels of access to their services and the levels of care they provide. The best configuration of EPAUs for optimal balance between cost-effectiveness, clinical, service and patient-centered outcomes remains unknown.

The recently published NICE guideline on Ectopic Pregnancy and Miscarriage (CG 154)[1] aimed to establish how different models of care within EPAUs might impact on service outcomes, clinical outcomes and women's experience of care. Fourteen studies were identified. The majority of studies (n=10)[4,5,6,7,8,9,10,11,12,13] were conducted in the UK. Of the included studies, two were cross-sectional studies[4,5], four were observational studies[6,14,15,16] that compared outcomes before and after establishment of an EPAU, and the remaining studies were descriptive[7,8,9,10,11,12,13,17]. The quality of evidence was described as low or very low[1].

Evidence from cross-sectional studies showed that in approximately half of the units, ultrasound scans are performed by sonographers only, whilst in less than a quarter of EPAUs, the scanning is done by medical, nursing or midwifery staff[1,4,5]. In the rest of the units, professionals from different disciplines perform ultrasound scanning. Regarding access to services, all units accept patients referred from other healthcare professionals, whilst only 51% of units accept self-referrals, and the majority of units (70%) provide a weekday service only[1,4,5]. There is a paucity of data regarding the best indicators for clinical and service outcomes, whilst women's views and experience of care were only included in two studies[1,11,13].

A pilot study to test the feasibility of a large-scale study was conducted in seven EPAUs in London. The units were selected on the basis of their size, staffing configuration and access to services. As there are no auditable standards against which the EPAU service can be assessed, the main service outcomes examined were proportion of follow-up visits, proportion of non-diagnostic ultrasound scans, proportion of visits for blood tests and proportion of women admitted to hospital. A total of 3769 women were included in this pilot study. The results are shown in Table 1.

Unit	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Follow-up attendances	26.6%	35.0%	39.8%	38.8%	36.4%	44.4%	41.1%
Non-diagnostic scans	8.0%	6.2%	8.2%	14.1%	10.6%	18.8%	30.0%
Attendances having blood tests	16.6%	11.9%	17.3%	16.2%	22.9%	28.3%	37.1%
Attendances resulting in admissions	3.9%	2.3%	4.8%	9.7%	7.9%	6.4%	9.7%
Attendances resulting in admissions for diagnostic work-up	0.0%	0.1%	0.0%	1.5%	1.4%	1.9%	2.6%

To evaluate the effects of the configuration of Early Pregnancy Assessment Units on clinical, service and patient-centered outcomes. It is hypothesized that in EPAUs with high consultant presence, the rate of hospitals admissions is lower than in units with low consultant presence.

3 OBJECTIVES

3.1 Primary Objective

To test the hypothesis that in EPAUs with high consultant presence, the rate of hospital admissions is lower than in units with low consultant presence.

3.2 Secondary Objectives

- To test the hypothesis that increased consultant presence in EPAUs improves other clinical outcomes, including number of follow-up visits, non-diagnostic ultrasound scans, negative laparoscopies and ruptured ectopic pregnancies requiring blood transfusion.
- To assess the effect of variations in opening hours and service accessibility on the overall admission rates and other clinical outcomes.
- To determine the optimal skill-mix to run an effective and efficient EPAU service.
- To examine the cost-effectiveness of different skill-mix models in EPAU.
- To explore patient satisfaction with the quality of care received in different EPAUs.
- To make evidence-based recommendations about the future configuration of EPAUs in the UK.

4 STUDY DESIGN

Multi-methods approach including: (i) cohort study of clinical outcomes, (ii) health economic evaluation including skill-mix and cost-utility model development, (iii) patient satisfaction survey, (iv) staff survey, (v) qualitative interviews with service users, and (vi) prospective hospital emergency care audit.

5 STUDY SCHEDULE

5.1 Randomisation procedure

The process for selecting the Units is described in section 8.1. There will be no randomisation of individual patients.

5.2 Definition of end of Study

The end of the study will be defined as the last 26-week/3-month follow-up visit for a participating patient.

The study will be considered closed when the last patient has reached this time-point, all data are complete and all data queries have been resolved.

6 CONSENT

Women who agree to participate will be asked by the triage (registered) nurse or midwife/research nurse or midwife/nurse sonographer/trial officer/research team lead/clinical research fellow/doctor to provide written consent before completing any study questionnaires. Members of staff who agree

to participate in the study will be asked by the local research co-ordinators to provide written consent prior to completing the staff survey.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

(i) Cohort study of clinical outcomes

All pregnant women (16 years of age and over) attending Early Pregnancy Assessment Units because of suspected early pregnancy complications.

(ii) Health economic evaluation

(iii) Patient satisfaction survey

(v) Qualitative interviews with service users

Pregnant women (16 years of age and over) attending Early Pregnancy Assessment Units because of suspected early pregnancy complications who agree to sign a written consent to participate.

(vi) Hospital emergency care audit

All women attending hospital emergency service because of early pregnancy complications over a period of three months.

(iv) Staff survey

All members of staff directly involved in providing early pregnancy care who agree to sign a written consent form to participate.

7.2 Exclusion Criteria

(ii) Health economic evaluation

(iii) Patient satisfaction survey

(v) Qualitative study

Women who are haemodynamically unstable, in severe pain and those who decline consent to participate in the study.

8 RECRUITMENT

8.1 Unit recruitment

Units will be approached to participate in the study. Meetings with the lead clinician and the key members of the team will be arranged to explain the study, participant recruitment and time scale. If a unit declines participation, the next centre of similar characteristics will be approached, until an alternative centre is recruited.

8.2 Patient recruitment

(i) Cohort study of clinical outcomes

Women will be provided with the study information leaflet as they register their attendance at the clinic reception. Once they have had sufficient time to read the information leaflet they will then be approached by the triage (registered) nurse or midwife/research nurse or midwife/nurse sonographer/trial officer/research team lead/clinical research fellow/doctor and asked to participate in the study. Women who agree to participate will sign a consent form at this point.
Demographic and routine clinical data will be collected from all women attending the EPAUs. In women who consent to the study their clinical data and questionnaires will be linked using their study number. The data from women who do not consent will be anonymised and the data collection forms will not leave individual hospital premises.

(ii) Health economic evaluation

Step 1. Women who consent to the study will be asked to complete the EuroQol-5D 5L (EQ-5D 5L) questionnaire and the Visual Analog Anxiety Scale (VAS-A) prior to their clinical assessment. They will also be asked to complete the same VAS-A at the end of their visit. In case of follow-up visits, women who consented to participate in the study will be asked to complete the VAS-A prior to and following review.
Step 2. Women who consent to the study will also be asked to complete the EQ-5D 5L questionnaire two weeks after discharge from the clinic.
Step 3. A sub-set of women, across all sites and stratified by outcome, will be asked to complete the EQ-5D-5L as well as a more detailed questionnaire about service use - the Client Service Receipt Inventory (CSRI) - 12 weeks post-discharge.

(iii) Patient satisfaction survey

Women who consent to the study will be asked to complete the Short Assessment of Patient Satisfaction (SAPS) measure as well as a condition-specific patient satisfaction questionnaire (modified Newcastle-Farnworth questionnaire) at two weeks post-discharge. Further information about the pregnancy, including the London Measure of Unplanned Pregnancy (LMUP) will also be collected.

(vi) Qualitative interviews with service users

Women who have taken part in the (iv) patient satisfaction survey and who have consented to being re-contacted in relation to a telephone interview will form the sampling frame for the qualitative interviews. A purposive, maximum-variation sample will be constructed to include women with different outcomes (e.g. ongoing pregnancy, miscarriage, ectopic pregnancy), different levels of reported satisfactions (e.g. above and below average satisfaction on SAPS), and experiences of EPAUs in different regions and with different service configurations. When re-contacted and invited for interview, women will have the opportunity to consent to an interview or to decline.

(vii) Hospital emergency care audit

Routine data for all women attending hospital emergency service due to early pregnancy complications will be collected over a period of three months at the time of site initiation. We

will collect data about the total number of attendances to EPAU and A&E departments. We will also collect data about the total number of emergency admissions, emergency operations and their outcomes, number of women receiving blood transfusions and number of admissions to intensive care units. Women will not be asked to consent to participate in this arm of the study.

Table 2 contains a summary of the different data strands of study, including types of different questionnaires and their timings.

Data strand	Data collection tool	Data source	When collected	Type of data
Cohort study of clinical outcomes	CRF	All women attending the service	At site initiation until 150 women have provided complete data	Anonymised
Health economic evaluation	EQ-5D 5L Q VAS-A VAS-A EQ-5D 5L Q CSRI Q EQ-5D 5L Q	Women attending the service who consent .	Upon arrival at EPAU After initial clinical assessment During follow-up visit, prior to and following clinical assessment 2 weeks post-discharge 3 months post-discharge	Identifiable
Patient satisfaction survey	SAPS Q LMUP Modified Newcastle Q	Women attending the service who consent	2 weeks post-discharge	Identifiable
Qualitative interviews wih service users	Interviews	Women attending the service who consent (purposive sample of 40)	Following analysis of clinical outcomes & SAPS Q	Identifiable
Hospital emergency care audit	Routine hospital data	All women admitted to hospital	Prospective for 3 months after site initiation	Anonymised

8.3 Staff recruitment

Members of staff directly involved in providing early pregnancy care will be approached and asked to complete a modified (shortened) version of the standard NHS staff survey. We aim to recruit 200 members of staff. It will be made clear that the responses to the survey will be anonymous.

9 STATISTICAL METHODS

Gareth Ambler is the study statistician who will be responsible for all statistical aspects of the study from design through to analysis and dissemination.

9.1 Sample size calculation

We plan to recruit 44 units, each contributing at least 150 patients. This will give us 90% power to detect a difference in admission of rates of 5% (8.5% vs 3.5%) between units with a low consultant presence and those with a high presence, at the 5% significance level. The results from our pilot study suggest that such a difference in admission rates is both clinically relevant and likely.

This sample size calculation is based on a simplified analysis where units are classed as having either low or high consultant presence based on a dichotomisation at the median level of consultant presence. The admission rates for the patients in the 22 units with "high" consultant presence are then to be compared to those from units with "low" consultant presence. A basic sample size calculation (that assumes no clustering) suggests that we require 946 patients in total (or 22 per unit). However, assuming a moderate level of clustering (ICC = 0.04) we would require 150 patients per Unit. Data collection for each unit will be for minimum seven days to ensure weekday/weekend variation is captured.

For the subsidiary data strands, the anticipated response rates are as follows:

(ii) Health economic evaluation

In the absence of prior knowledge of the expected values and standard deviations of costs and effects (in this case, QALYs) it is not possible to formally estimate a required response rate. Therefore, we have taken a pragmatic approach to determining the number of resource use questionnaires to collect. Our aim is to balance the collection of sufficient data to make inferences about cost-effectiveness against the burden on women of being asked to complete data collection forms shortly after the loss of a pregnancy.

Questionnaires will be sent to randomly chosen women, selected from those who have given prior consent for further contact. The sample will be stratified using the same criteria as used to select participating EPAUs. We anticipate that 320 completed questionnaires will provide sufficient data.

An algorithm and approach to sampling similar to that used to select units for participation in the study, will be used to select women to be approached to complete the resource use questionnaire. The key factors used to sample will be consultant presence (at four levels), weekend availability and number of patients attending. Each stratum of each key factor will be equally represented. That is, 80 women will be in stratum 1 for consultant presence, 80 will be in stratum 2, and so on. Likewise, 160 women will be in stratum 1 for weekend opening and 160 will be in stratum 2, and similarly for number of patients attending a unit. Women will be approached to complete the resource use questionnaire until we achieve 320

responses balanced across factors and strata.

In order to accurately capture the workforce resources needed to run each EPAU, we will prospectively collect data on members and grades of staff involved in providing care as well as the time spent providing this care. Consultant presence will be collected prospectively for each session/day that data will be collected for (i.e. a record of whether a consultant is physically present in the unit reviewing patients will be collected for every session for which we are collecting data).

(iii) Patient satisfaction survey

Our study population will include 6600 women (150 x 44 units, see above). If our response rate is 30%, then a 95% confidence interval (for a yes/no question) will have a margin of error of at most 2.2%. If the response rate is just 10%, then the error will be at most 3.8%.

(iv) Staff survey

We expect that there will be approximately 200 staff members in the sample of 44 units. If our response rate is 50%, then a 95% confidence interval (for a yes/no question) will have a margin of error of at most 10%.

(v) Qualitative interviews with service users

Forty interviews will be carried out with EPAU service users. This calculation is based on the needs of the intended maximum variation sample[18,19] (enabling representation by region, pregnancy outcome, and reported level of satisfaction) and will provide a wealth of qualitative data for analysis.

(vii) Hospital emergency care audit

Results from the pilot study and the initial clinician survey showed that the average number of women reviewed in different EPAUs across the country is 105 per week. We are planning to collect hospital statistics data over three months, which should provide us with sufficient numbers to have enough power to detect significant differences in rare outcomes such as the proportion of negative laparoscopies, transfusion rates and ITU admissions.

9.2 Planned recruitment rate

The selection of the participating Early Pregnancy Units was completed in April 2016. Each unit will collect data until a total of 150 patients have been recruited and for minimum seven days. Units will start and finish collecting data at different times (staggered data collection) and data will be collected over approximately six months.

9.3 Statistical analysis plan

9.3.1 Primary outcome analysis – Cohort study of clinical outcomes

The primary analysis will investigate whether consultant presence is associated with admission rate. We will perform a patient-level analysis and hence will use hierarchical logistic regression models that allow for patient clustering within EPAUs. Consultant

presence will be modelled as a continuous variable. The use of regression modelling will allow us to adjust for confounding factors, which may be associated with higher admission rates. The results of this analysis will be reported in terms of odds ratios (with corresponding confidence intervals and P-values) to indicate the degree of association. All model assumptions will be checked. Specifically, level 2 residuals will be checked for normality and linearity assumptions will be checked. The ICC, which indicates the degree of clustering within EPAUs, will also be reported. Multiple imputation will be used if there is a high degree of missing data.

Regarding analysis, our first step will be to characterize the amount of missing data and to identify patterns of missingness, if they exist. Simple descriptive analyses will be used to describe the missingness of each (important) variable, then tabulations and logistic regression modelling will be used to explore whether the missingness in one variable depends on specific patient characteristics. These analyses may give us an insight into whether we can assume that the data are 'missing at random'. Under a 'missing at random' (MAR) assumption, we may model the data, taking account (adjusting) of those variables associated with missingness. This will lead to valid inferences (if our MAR assumption is correct). In addition, we will consider using multiple imputation methods to impute the missing values. This will be achieved by using 'imputation via chained equations'[20]. Under a MAR assumption, this method imputes missing values (using regression models) based on the values of other variables. Multiple imputed datasets are produced to account for the uncertainty involved in the imputation process. These datasets are then analysed separately and the results combined. It is likely that these imputation models will make use of the clinical data, which are expected to be near complete. If the 'missing at random' assumption is thought to be untenable, we will use a few approaches to deal with this issue. Firstly, though, it will be important to understand the possible reasons for the missing values to better design the sensitivity analyses that follow. Then, we will investigate the use of relatively complex imputation models as part of the multiple imputation exercise. The idea here is that by including more variables in the imputation model, the MAR assumption should become more plausible[20]. We will also use sensitivity analyses to check the robustness of our results. Specifically, we will impute the missing data under various ('missing not at random') scenarios and see how the results of our primary analyses change.

9.3.2 Secondary outcome analysis

The analyses of the secondary outcomes (number of follow-up visits, non-diagnostic ultrasound scans, negative laparoscopies, estimated blood loss at surgery and ruptured ectopic pregnancies requiring a blood transfusion, patient satisfaction) will follow a similar pattern although the type of regression model will be tailored for the specific outcome measure (e.g. hierarchical Poisson/linear regression will be used to analyse number of follow-up visits). Regression modelling will also be used to analyse the effect of opening hours and service accessibility on the overall admission rates and other clinical outcomes. Again, the type of regression model will depend on the clinical outcome and opening hours / service accessibility will be treated as exposure variables.

Health Economic analysis

The economic evaluation will comprise two parts:

- a within-study analysis, and
- a longer-term, model based, analysis.

The within-study analysis will focus on the costs and outcomes during the study period and will be based on the data collected during the study. The longer-term model based analysis will supplement the study data with data from the literature, particularly on patient outcomes. These additional data will be used to estimate the cost-effectiveness of different staffing configurations when longer term outcomes are taken into consideration.

In each analysis we will examine the cost-utility of different skill-mix configurations for staffing EPAUs. Outcomes for each analysis will be 1) patient quality of life, measured as quality adjusted life years (QALYs) and 2) admissions avoided.

Costs will be estimated from a societal perspective (capturing costs to the NHS, social services and patients). Results will be reported as the incremental net benefit of the modelled skill-mix configurations, and incremental cost-effectiveness ratios.

Uncertainty will be captured in the analyses through probabilistic sensitivity analysis and reported using cost-effectiveness acceptability curves, showing the likelihood a particular skill-mix model will be cost-effective over a range of values of the societal willingness to pay for a QALY.

In this section, we detail how we will collect and analyse data for the economic evaluation and how this will link with the skill-mix modelling.

Skill-mix model development:

The services delivered by a given EPAU are determined by two broad factors:

1. the workforce delivering the required care, and
2. the clinical approach used to deliver that care (for example the thresholds for certain tests to be offered may be different even in configurations where the staff make-up is similar).

Using the clinical and operational data collected as part of the cohort study of clinical outcomes, we will identify skill-mix models appropriate for further consideration in a cost-utility analysis. This first stage of analysis will define appropriate EPAU skill-mix configurations for assessment in cost-utility analysis. The set of alternative staffing configurations will be used to estimate the expected costs of different skill-mix models, based on what is already known about the studied EPAUs. These models will consider both skill-mix and other factors that determine the cost of delivery local services.

The costs for each EPAU to deliver services will also vary according to each configuration as these will be dependent on the make-up of the local workforce as well as the local costs of

premises and equipment. While care pathways may be consistent across the country as a result of the nationally adopted guidelines, the scale and size of each EPAU will be different due to the service requirement of each locality due to population size, epidemiological factors and local socio-economic characteristics (such as ethnicity, levels of deprivation and education). This means that the workforce size and EPAU cost required to meet the service requirement will be locally dependent, and we will account for variation in costs in the analysis.

Within the skill-mix model we will consider the level of consultant presence, as well as the number and grade of other clinical and support staff available. The costs of implementing any configuration will include both the quantity of each skill set (consultant, junior doctor, nurse etc) required and the coverage time for which they are required. Another important factor to consider in skill-mix models will be case mix. A complex case mix may create a workload equivalent to that in a bigger unit with a less complex or complicated case mix.

Development of optimal skill mix model to run

Cost-utility analysis overview:

Using the skill-mix model analysis we will then evaluate the cost utility of the set of identified potentially optimal skill-mix configurations. This analysis will combine the results of the skill-mix modelling configurations (with associated costs), patient outcome data, patient resource use data and data on additional costs to patients, social services and the NHS not already captured in the EPAU unit configuration costs. Results of the economic evaluation will be reported in standard metrics, including:

- The incremental cost-effectiveness ratio (ICER) of an additional admission avoided, (cost per additional avoided)
- The ICER based on quality adjusted life years (cost per QALY gained), and
- the net benefit statistic.

Sensitivity analysis will be used to test assumptions about the model structure, to explore the generalizability of the results and to capture the underlying uncertainty in the sample data. Probabilistic sensitivity analysis will be used to capture the uncertainty arising from the sampled data, with model parameters defined as probability distributions and Monte Carlo simulations used to simulate repeated trials. Structural uncertainty in the model (for example, relating to variability in individual skill-mix configurations or local staff availability) will be explored using one-way and scenario analyses. Additional one and two-way analyses will be used to explore further the generalisability of the results.

Primary within-study analysis

The primary economic evaluation will be a within-study analysis. As described above, in the analysis we will estimate incremental cost-effectiveness ratios for the two main outcomes of interest, patient quality of life (in QALYs) and admission rates. These will be reported together with associated Bayesian credible intervals, based on the data collected in during

the study period. For this analysis data will be drawn as far as possible from the study data. Monte Carlo simulation methods will be used to construct a cost-effectiveness acceptability curve, based on the expected net benefit statistic, to estimate the probability that the intervention is cost-effective for a range of values of societal willingness to pay per QALY. We will also subject the results to extensive deterministic (one, two, and multi-way) sensitivity analysis.

The analysis process will be as follows: Initial data exploration will be conducted using standard frequentist statistical approaches. First we will compare baseline costs and other factors between groups to determine if any of the baseline characteristics predict costs. Where there are differences appropriate methods will be used to standardise/adjust for these. Unadjusted costs and outcomes will be estimated and reported. Regression analyses will be used to adjust for differences in baseline characteristics and adjusted values will also be reported. Estimates of skewness will be calculated for all resource use variables. As resource use data are commonly skewed, appropriate regression methods will be required (eg GLM) to account for this.

We will explore whether there are baseline characteristics across each group that explain differences in costs. This will be used to explain how costs are linked to baseline characteristics and the intervention. This will help us understand skill-mix variation effects holding everything else constant. It can also help us understand what the drivers of patient costs are and whether they are associated with any between group differences. Coefficients and p-values will be reported for each model tested.

Once we have explored the data and assessed for any important difference in baseline characteristics cost-effectiveness analysis can be undertaken. Unadjusted data will be used for the cost-effectiveness analysis. Simulation methods as described by O'Hagan and others[22] will be applied. As is common with healthcare data, costs are expected to be skewed due to a small number of patients who typically consume a disproportionately large level of resources. As a result, the assumptions required for standard statistical approaches based on normally distributed data do not hold. A Bayesian parametric approach to analysis of costs will be followed to address concerns arising from the expected non-normality of the data.

Changes in reported anxiety measured using the visual analog scale will also be evaluated. Anxiety measures will be taken at the baseline data collection point, at the end of the initial visit to the EPAU prior to discharge and then at any clinic follow-up appointments. In the absence of an accepted minimally important difference in anxiety scores a standardised scoring based on Cohen effect sizes will be applied, with 0.2 assumed to be 'small' effect size, 0.5 medium effect size and 0.8 a large effect.

Secondary modelling analysis

Additional longer-term modelling will also be undertaken based on the sub-sample of women followed up at 26 weeks gestation or 3 months post-pregnancy loss. For this analysis, a decision analytic model will be developed, based on the sample data. The model will be used to combine all relevant input data on skill mix variation along with patient

outcomes and costs as measured at 26 weeks/3 months. As with the within-study analysis cost-effectiveness results will be reported as a) the incremental cost per QALY gained and b) the incremental cost per admission avoided. Again, we will also report the net-benefit statistic. Uncertainty in the model parameters will be captured by probabilistic sensitivity analyses using Monte Carlo simulations. Overall decision uncertainty will be calculated and presented using cost-effectiveness acceptability curves. Additional one-way, two-way and scenario sensitivity analysis will be undertaken to test assumptions made in the initial model structure (these assumptions are not subject to parameter uncertainty but may influence results).

Analysis of qualitative interview data

The analysis of the qualitative interview data will be carried out using the Framework method[24], utilising NVivo software. The Framework method has five stages (1) familiarization, 2) identifying a thematic framework, 3) indexing; 4) charting, and 5) mapping and interpretation) and allows cross- and between-case analysis. The focus of the analysis will be to examine the range of women's experiences of EPAU services, and to explore how aspects of service provision relate to women's positive and negative experiences. Features of service provision shown to be important in previous research (e.g. choice, empathetic care) will also be included, investigating how women perceive these and how/if these relate to EPAU service configuration.

10 PATIENT AND PUBLIC INVOLVEMENT (PPI)

The research question was identified by the NICE Guideline (CG 154)[1] on "Ectopic Pregnancy and Miscarriage"; the NICE guideline committee had two lay members on the guideline group (25%) who played a major part in deciding on the recommendations. Patient Opinion, the independent feedback platform for healthcare, was searched in order to identify patients' opinions on early pregnancy care. A patient questionnaire with a set of open and closed questions, developed based on the feedback of users' experiences of EPAUs from Patient Opinion was developed to identify service user views about the set up of an EPAU. The questionnaires were distributed to different units to order to capture the opinions of service users. We also held a public focus group attended by service users.

This study has been endorsed by the Miscarriage Association, the Ectopic Pregnancy Trust and the Association of Early Pregnancy Units. Mrs Ruth Bender Atik from the Miscarriage Association is a co-applicant and represents patient/and public views. She is involved with the management, conduct, analysis and dissemination of the study findings. The information leaflets and consent forms have been reviewed by patients in order to improve the clarity of these documents. Research findings will be disseminated at the Annual Meeting of the AEPU, and via communications of the Miscarriage Association and Ectopic Pregnancy Trust.

11 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The research costs for the study have been supported by National Institute for Health Research (NIHR), Health Services and Delivery Research Programme (HS&DR), Grant number 14/04/41.

12 DATA HANDLING AND MANAGEMENT

The data will be handled and summarised by MedSciNet in accordance with the UK Data Protection Act 1998 as well as UCL Information Security Policy and Trust Information Governance Policy.

In detail, MedSciNet uses an SSL (Secure Sockets Layer) protocol that secures communication between server and client and prevents anyone from intercepting and reading the data between them. The certificates (SSL Certificate Authority) are managed by GlobalSign, one of the world's leading Certificate Authority (http://www.globalsign.com/). User (or person) is identified by his/her unique user name in the system and the user identity is verified (or authenticated) by user name and password. Administrators can use built-in user account management system, which helps to manage user-specific data (such as passwords, expiration dates, etc.). A two-factor, two-channel authentication, implemented using SMS over mobile devices, is available upon request. Authentication using mobile devices, such as mobile phones and PDAs, transforms these devices into One-Time Password token devices. Authentication in such a way provides strong authentication protection to system users without deploying additional, dedicated hardware tokens. Particular user has a set of rights in the system – s/he can perform only these functions that s/he is authorized to do, while system logs every attempt to log-in to the system and every change of data (what data are being changed, who is trying to change and when) is logged too.

The detailed analysis plan will be formally agreed by the co-investigator group with input from the Study Steering Committee before data analysis is undertaken.

13 RECORD KEEPING AND ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of study report. The documents will be stored in a secure locked cabinet with access restricted to specified staff. The study database will be kept on the UCL secure server. Another copy will be kept on a password protected encrypted disc which will also be locked in a secure cabinet.

The Chief Investigator is responsible for the secure archiving of essential study documents (for each site, if multi-site study) and the study database as per their trust policy. All essential documents will be archived for a minimum of 5 years after completion of study.

Destruction of essential documents will require authorisation from the Sponsor.

14 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance to NIHR requirements secured through awarded funding.

The study was deemed to require regulatory approval from an Ethics Committee. Their approval will be obtained before the study commences.

15 ASSESMENT AND MANAGEMENT OF RISK

This is an observational non-interventional study and all women included will receive standard hospital care. On the basis of this, the study is categorised as:

• Type A = No higher than the risk of standard medical care.

16 MONITORING AND AUDITING

The Chief Investigator will ensure there are an adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

- **Study Steering Committee (SSC):**
  The Study Steering Committee will provide advice on the overall conduct of the study. Membership is drawn from stakeholders with knowledge and experience of early pregnancy services in the UK. The SSC is to meet twice annually. The members are listed below:

  - Independent Chair: Prof Pat Doyle (London School of Hygiene and Tropical Medicine)
  - Clinicians: Miss Cecilia Bottomley (Chelsea & Westminster Hospital), Miss Marjorie Maclean (Glasgow Royal Infirmary)
  - Epidemiologist: Mr Brad Manketlow (University of Leicester)
  - Health Economist: Dr Hannah-Rose Douglas (London School of Hygiene and Tropical Medicine)
  - Commissioner: Dr Elizabeth (Liz) Bradley, Maternity and Gynaecology Clinical Lead, Camden CCG, London.
  - Patient/Public Representative: Ms Alex Peace-Gadsby (Ectopic Pregnancy Trust)
  - We will also invite two observers; a representative of UCL as the sponsor and a representative from the research network.

- **Expert Reference Group:**

  The aim of Expert Reference Group is to review the study protocol and provide critical feedback to the Study Management Group regarding scientific quality, methodology and feasibility of the study. The members of the group are:

- Mr Roy Farquharson (Chair, Consultant Gynaecologist), Liverpool
- Prof Siobhan Quenby (Professor of Obstetrics), Warwick
- Dr Tim Baruah (A&E Consultant), London
- Ms Allison Farnworth (Research midwife), Newcastle
- Dr Lyann Gross (GP), London

- **Lay Reference Group:**
  The aim of Lay Reference Group is to review the study protocol and provide feedback to the Study Management Group regarding methodology and feasibility of the study, with particular emphasis on the quality of patient information and involvement. Chairperson of the Lay Reference Group is Ms Ruth Bender Atik and it includes four patients/service users, as identified by the Miscarriage Association and Ectopic Pregnancy Trust.

17 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files.

18 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

19 ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The study master file will be archived at UCL in accordance with the UCL Standard Operating Procedure 10 Archiving of Investigator Site File (ISF) and Pharmacy Site File (PSF). It will be archived for a minimum of 5 years from the study end, and no longer than 30 years from study end.

20 PUBLICATION POLICY

The Chief Investigator will co-ordinate dissemination of data from this study. All publications using data from this study to undertake original analyses will be submitted to the SSC for review before release.

To safeguard the scientific integrity of the study, data from this study will not be presented in public before the main results are published without the prior consent of the SSC. The success of the study depends on a large number of health care professionals. For this reason, credit for the results will not only be given to the committees or central organisers, but to all who have collaborated and

participated in the study. Acknowledgement will include all local co-ordinators and collaborators, members of the oversight and advisory committees, and staff.

Authorship at the head of the primary results paper will be decided depending on the contribution of individuals to setting up, running and successfully concluding the study.

Outcomes of the study will be available on Researchfish (www.researchfish.com). In accordance with NIHR policy, a copy of the paper will be sent to the HS&DR co-ordinating centre prior to publication and a copy of all manuscripts accepted for publication will be deposited with UK PubMed Central in order to be made freely available. A copy of the journal article will be available on request from the research team.

21 REFERENCES

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