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STOP-OHSS

STOP OHSS

STOP-OHSS Protocol

STOP-OHSS (Shaping and Trialling Outpatient Protocols for Ovarian HyperStimulation Syndrome): A randomised controlled trial to assess the clinical and cost-effectiveness of earlier active outpatient management of Ovarian HyperStimulation Syndrome.

RESEARCH PROTOCOL
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STOP-OHSS (**S**haping and **T**rialling **O**utpatient **P**rotocols for **O**varian **H**yper**S**timulation **S**yndrome): A randomised controlled trial to assess the clinical and cost-effectiveness of earlier active outpatient management of Ovarian HyperStimulation Syndrome

STOP-OHSS Protocol

This document describes a clinical trial and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known appropriate stakeholders in the trial.

Contents

Abbreviations

Definition of terms

AE	Adverse Event
aHR	Adjusted Hazard Ratio
ART	Assisted Reproductive Treatments
BMI	Body Mass Index
CCC	Confirmation of Capacity and Capability
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTA	Clinical Trial Authorisation
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DPA	Data Protection Act
eCRF	Electronic CRF
FBC	Full Blood Count
GCP	Good Clinical Practice
GP	General Practitioner
GnRH	Gonadotropic-releasing Hormone
hCG	Human Chorionic Gonadotropin
HEAP	Health Economics Analysis Plan
HFEA	Human Fertilisation and Embryology Authority
HRA	Health Research Authority
HRQL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICH	International Conference on Harmonisation
ICSI	Intracytoplasmic Sperm Injection
IP	Inpatient
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
IUI	Intrauterine Insemination
IVF	In Vitro Fertilisation
LOS	Length of Stay
LPLV	Last Patient Enrolled on Trial
MN	Medical Notes
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
OHSS	Ovarian Hyperstimulation Syndrome
OP	Outpatient Paracentesis
OPt	Outpatient
OR	Odds Ratio
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
PSS	Personal Social Service

QALY	Quality-Adjusted Life Years
QRI	Quintet Recruitment Intervention
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
ScHARR	School of Health and Related Research
SOP	Standard Operating Procedure
SR	Self-reported
STH	Sheffield Teaching Hospitals
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Usual Care
UCL	University College London

1. General study information

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The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.7 Protocol amendments

Protocol Version	Changes made
VX	None

Trial Summary

Study title	STOP-OHSS (Shaping and Trialling Outpatient Protocols for Ovarian HyperStimulation Syndrome): A randomised controlled trial to assess the clinical and cost-effectiveness of active management of Ovarian HyperStimulation Syndrome.
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	The NIHR Health Technology Assessment Programme
ISRCTN	71978064
Project start date	01 December 2019
Project end date	01 December 2024
Hypothesis, aims and objectives	Hypothesis: The use of Outpatient Paracentesis (OP) in the management of moderate or severe OHSS will result in earlier resolution of symptoms and avoid the need for hospital admission, when compared with usual care. Aim: The study aims to establish the clinical and cost-effectiveness, safety, and acceptability of OP as an active management for women with moderate or severe OHSS, in a multi-centre adaptive RCT with internal pilot to assess the feasibility of conducting the RCT. Objectives: Primary objective: Establish whether OP reduces the rate of OHSS related hospital admissions in those presenting with moderate or severe OHSS compared to usual care. Secondary objectives: 1. Establish whether OP prevents the escalation of OHSS severity compared to usual care 2. Establish whether OP reduces the time taken for OHSS symptoms to resolve compared to usual care 3. Establish the safety of OP as an active intervention for moderate or severe OHSS compared to usual care 4. Explore whether OP would improve patient satisfaction and quality of life of participants compared to usual care 5. Establish whether OP is cost-effective compared with usual care by examining healthcare resource use and patient costs 6. Facilitate the feasibility of conducting the RCT by identifying problems with the conduct of the RCT during the internal pilot, so that solutions can be instigated.

Study design	Pragmatic, two-arm, parallel-group, adaptive, open label, superiority, confirmatory, group sequential, individually RCT with one interim analysis for futility early stopping. Participants will be randomised (1:1) to receive outpatient paracentesis (OP) plus increased self-monitoring or conservative management (usual care).
Internal pilot and interim analysis	There is a STOP-GO point on the trial as part of the internal pilot following 15 months of recruitment to assess feasibility aspects of conducting the trial. Targets cover participant recruitment, retention and intervention delivery. An interim analysis will be performed for futility early stopping when 65% (73 per arm) of the maximum required participants have accrued primary outcome data on hospitalisation. Early stopping for efficacy is not permitted.
Setting	National Health Service (NHS) and private fertility centres across England and Scotland. Both private and NHS sites included.
Participants	A total of 224 women with moderate or severe (early or late) OHSS will be randomised to the trial. The women will be undergoing In vitro fertilisation (IVF) (including intracytoplasmic sperm injection (ICSI)) or intrauterine insemination (IUI). Inclusion criteria: 1. Women presenting with moderate or severe OHSS as defined by the trial. 2. Patients able and willing to attend weekly follow-up appointments in person or remotely, daily remote appointments/phone calls, and able to undertake self-monitoring at home. Exclusion criteria: 1. OHSS-related exclusion criteria: a. Significant pain* or vomiting requiring hospitalisation b. Pulmonary embolism c. When in the judgment of the clinician, the patient's condition is severe enough to warrant admission to a High Dependency Care Unit (such as Critical OHSS as defined in the Royal College of Obstetricians and Gynaecologists (RCOG) green-top guidelines) and therefore not suitable for outpatient management. 2. Non-OHSS related medical conditions: A concurrent medical condition requiring immediate inpatient management 3. Patients who have been previously randomised but later present with moderate or severe OHSS

	symptoms in subsequent cycles after their initial trial involvement. 4. Participation in other trials involving ovarian stimulation or ovarian response. *Significant pain will require clinical judgement but may be guided by whether the patient is able to manage the pain at home using 'over the counter' analgesia or if there are any clinical concerns regarding other conditions potentially contributing to the pain (e.g. ectopic pregnancy)
Intervention and control groups	Control (usual care): Conservative management Intervention: Outpatient paracentesis (OP) plus increased self-monitoring
Primary outcome	OHSS related hospitalisation for at least 24 hours within 28 days of randomisation.
Secondary outcomes	• Need for hospitalisation (OHSS related) within 28 days of randomisation – independent blinded central assessment • Time to resolution of OHSS assessed within 28 days of randomisation • Progression of OHSS severity within 28 days of randomisation • Live birth, pregnancy outcomes, neonatal death and serious adverse events including congenital abnormalities in the new-born within 13.5 months of randomisation • The occurrence of thrombosis or embolism and significant infections requiring antibiotic treatment or hospitalisation within 90 days of randomisation • Adverse Events within 28 days of randomisation • Patient satisfaction assessed using the Client Satisfaction Questionnaire 8 (CSQ-8) based on total scores at 28 days post randomisation • EQ-5D-5L participant quality of life daily and at 28 days post randomisation • Health resource use and patient costs at 28 days post randomisation
Duration of recruitment period and first enrolment date	31-month recruitment period from February 2022 to August 2024 First enrolment date expected to be February 2022
Duration of follow-up	31-month follow-up period from March 2022 to September 2024
Target sample size	A total of 224 (112 per arm) assuming a 41% usual care hospitalisation rate, 20% targeted reduction in hospitalisation rate attributed to the intervention, 0% dropout rate, a 90% power for a 2.5% one-sided test, and one interim analysis when 65% (73 per arm) have accrued primary outcome data for non-binding futility early stopping.

Definition of end of trial	After 28 day follow-up for the last patient enrolled on the trial (LPLV). Secondary outcomes measured after 28 days will involve data collected from medical notes only.

2. Introduction

Ovarian hyperstimulation syndrome (OHSS) poses one of the greatest risks to women undergoing assisted reproductive treatments (ARTs), including in-vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) and intrauterine insemination (IUI). OHSS usually occurs in women who have over responded to ovarian stimulation drugs and is triggered by the effect of human chorionic gonadotropin (hCG) either administered during the course of treatment to trigger maturation of the oocytes (the eggs) or produced naturally by a resulting pregnancy. The ovaries become enlarged and cystic and fluid leaks into various body cavities. Currently, treatment is only usually provided once the condition has progressed to a severe state and the patient requires inpatient treatment (1). OHSS can be classed as mild, moderate, severe or critical. Moderate cases involve the build-up of fluid in the abdomen (called ascites), increased ovarian size, and abdominal pain. In severe cases, fluid retention and dehydration can lead to changes to the constitution of the blood (haemoconcentration and hypoalbuminemia); in critical cases further fluid retention can lead to respiratory distress, thrombosis, disturbed renal and liver functions, and rarely death (2).

OHSS can be further clinically classified into early and late. Early OHSS is usually caused by the ovarian stimulation drugs given during treatment, and usually occurs within 7 days after the final drug (called hCG) is given. Late OHSS usually occurs 10 days or more after the administration of hCG and is caused by endogenous hCG of a resulting pregnancy. The late type is usually more difficult to control, runs a longer course and is more severe (3). Although mild forms of OHSS are fairly common (approximately 1 in 3 women undergoing IVF treatment), more severe OHSS, although less common (up to 8% for combined moderate and severe OHSS) (1) can have a significant impact on a woman's health resulting in prolonged hospitalisation and posing a significant economic burden on both patient and National Health Service (NHS) resources.

With over 68,000 IVF cycles performed in the UK in 2016 alone, resulting in potentially over 5000 women suffering from severe OHSS, the burden of the problem becomes evident (1). Although the mean hospital stay is approximately 3 days (3), the duration of stay can be much longer (4). Admission often results in a significant number of laboratory investigations and blood tests being performed on a daily basis. Care often involves multi-disciplinary input and occasionally high dependency or intensive care therapy in women with critical OHSS. Furthermore, complications such as venous thromboembolism can have long term health effects that last well beyond the length of the pregnancy. Therefore, the burden on women of being admitted with OHSS for an undetermined period cannot be overstated and neither can the burden of investigations and inpatient medical interventions on the NHS.

Currently, clinical practice usually involves monitoring the patient until the condition becomes severe, at which point the patient is admitted to hospital, as recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) green-top guideline (1). This in-patient management often includes drainage of ascitic fluid (paracentesis) which can result in a significant improvement of the condition and an improvement in renal blood fluid, urine output and reversal of the haematological abnormalities (5–7) which improves symptoms and the overall condition.

OHSS is the most serious and potentially fatal complication of assisted conception treatment with a significant effect on women and their families and poses a significant challenge to current and future NHS resources. The burden of OHSS is expected to

potentially increase in the future given current fertility trends, as evidenced by Human Fertilisation and Embryology Authority (HFEA) data, there has been a consistent increase in the number of IVF cycles provided in the UK since 1991 with a 4% increase in 2016 compared to 2015 (8). Given NHS England's mandate to reduce emergency admissions and the current significant economic burden on the NHS, it is important to look into novel approaches to improve outcomes and the management of complications associated with IVF (9).

2.1 Trial definitions of the categorisation and severity of OHSS

Categorisation of OHSS – this is classed as early or late as follows:

Early OHSS is caused by the ovarian stimulation drugs given during ARTs and occurs usually up to 7 days of the final trigger drug (hCG) being given.

Late OHSS usually occurs 10 or more days after the trigger drug is given.

Where a patient presents at 8 or 9 days clinical judgement will be used to classify the early or late OHSS.

Severity of OHSS – this is classed as mild, moderate, severe, or critical as follows, based on the classification recommended by the RCOG:

Mild OHSS:

- abdominal bloating
- mild abdominal pain
- ovarian size is usually below 8cm.

Moderate OHSS:

Patients do not meet the criteria of severe (described below) and have fluid accumulation in abdomen (ascites), confirmed by ultrasound scan. The following symptoms may also be present:

- Moderate abdominal pain
- increased ovarian size of usually 8-12cm
- nausea with or without vomiting

Some degree of clinical judgement may be needed to confirm the diagnosis of moderate OHSS.

Severe OHSS:

- Patients have fluid accumulation in abdomen (clinical ascites/clinically detectable fluids), confirmed by ultrasound, with or without hydrothorax
- The main distinguishing features are any of the following:
    - low urine output (oliguria)(< 300 ml/day or < 30 ml/hour)
    - haematocrit >0.45, (confirmed via full blood count – FBC test)
    - ovarian size >12cm.

Critical OHSS:

- Clinically obvious ascites, with one of the following features:
    - the patient has a tense ascites or a large hydrothorax
    - haematocrit level >0.55 (confirmed via FBC test)**
    - a white cell count of over 25000/ml (confirmed via FBC test)
    - anuria (very little/no urine) (< 100 ml/day)

- thromboembolism
- acute respiratory distress syndrome

** haematocrit level is the most important measurement

2.2 Rationale for current study

2.2.1 Evidence from relevant previous studies

A key 2018 systematic review by Gebril, *et al*. (10) has identified relevant studies and informed this research.
Several studies have suggested that outpatient paracentesis can reduce progression of OHSS and prevent the need for hospitalisation if undertaken prior to the condition requiring intensive in-patient treatment. Small retrospective case series studies (11,12) and a larger uncontrolled study (13) have suggested that frequent trans-vaginal paracentesis can reduce the need for hospitalisation to between 2.9% and 14% of patients. Another small prospective cohort study identified patients with moderate OHSS who were at risk of this progressing to severe OHSS, and reduced this progression with only 1 to 3 paracentesis procedures (14). There is also some evidence suggesting that trans-abdominal administration of paracentesis can prevent inpatient hospitalisation compared to those managed supportively (15). Furthermore, preliminary studies have safely and effectively managed patients in the outpatient setting by using a pigtail catheter to drain ascetic fluid (16,17). All of the discussed studies have still achieved high pregnancy rates of 68% (15) and 100% (14).

Similar evidence exists from oncology studies to support this outpatient management strategy that have shown the safety and feasibility of outpatient drainage of ascites in women with malignant ascites (18). Modelling has also suggested that it would be more cost-effective to treat patients with moderate or severe OHSS with early outpatient paracentesis (OP), compared to less active management and inpatient admission (4).

In summary, preliminary results have been encouraging and suggested promising safety and effectiveness of OP (11–15,17). However, this needs to be evaluated in a robust and adequately powered RCT within and outside the NHS taking into consideration variabilities in practice across fertility units.

2.2.2 Rationale

OHSS is the most serious and potentially fatal complication of assisted conception treatment and given that fertility services are likely to be used more and more, the burden of OHSS will increase. More severe OHSS is currently managed conservatively with in-patient or emergency admissions, which poses a significant economic burden on the NHS. Previous studies have indicated that novel approaches including increased monitoring and paracentesis are potentially safe and effective at treating OHSS and reducing related hospitalisations. However, there is a lack of large RCT to provide most reliable evidence to support the efficacy, safety and cost-effectiveness of early OP and encourage cultural change in the way that OHSS is treated if found to be effective and safe.

The trial will look at providing the same supportive treatment provided to severe OHSS as an inpatient in an outpatient setting, and will also target women with moderate OHSS who are not always actively treated at present. The hypothesis as supported by available literature is that outpatient interventions at this stage may decrease progression into severe OHSS. The main benefit from this trial is likely to be achieved through targeting patients with moderate OHSS. The main burden of

OHSS lies in the fact that treatment of severe OHSS can be prolonged and of unpredictable duration. Once the condition enters into the severe stage aggressive clinical management is required as little can be done to provide supportive treatment and await spontaneous resolution. Late OHSS tends to be more difficult to control and more severe, however, we expect the clinical effect of paracentesis to be similar between early and late OHSS. If an active outpatient intervention is shown to be acceptable, safe, clinically effective and cost effective, then it may remove this element of unpredictability with clear benefits to women, their families and the NHS.

Additionally, a significant amount of public interest in OHSS exists. Between 2017 and 2018 alone, there were at least three parliamentary questions regarding OHSS (19–21). Furthermore, a recent proposal was made in Parliament for a change in the HFEA act regarding Welfare of the Woman focusing on the prevention of OHSS by Siobhain McDonagh MP (22). In this parliamentary debate, it was noted that a recent investigation by the Press showed that in 2015 there were 836 emergency hospital admissions for severe OHSS despite the HFEA database recording only 60 cases in that time period. This strongly suggests the possibility that there is under reporting of women with severe OHSS. This may be as a result of several factors but could partially be because of loss to follow up due to women being admitted in other units other than those where they had their treatment. In this study, we will not only include fertility units but also work with the secondary and tertiary hospitals where these women may be admitted to collect outcome data.

2.2.3 Challenges to the conduct of this trial and mitigation

At the moment, the majority of clinicians would intervene for severe OHSS by hospital admission and inpatient management (1). To be able to manage these patients in an outpatient setting does require a level of confidence and change in attitudes that can only be achieved by providing high quality evidence within a large RCT to show if the procedure is clinically effective, cost effective, and more importantly safe.

The cultural change for women with OHSS would also be quite significant. The acceptability of outpatient management compared to inpatient management is likely to vary largely between women depending on geographical location and social circumstances. Where some women may find admission to hospital more convenient others may find this more disruptive and see a clear advantage of being managed in an outpatient setting. We have undertaken a feasibility study which explored patient and healthcare professional views and experience of the active management intervention and will measure acceptability of the active management intervention and usual care in this study. We have strongly involved patient groups and particularly women who have personally experienced OHSS at every stage of development of this protocol (see section 22).

2.2.4 Research question and hypothesis

Our main research question is:

What is the clinical and cost effectiveness, safety profile and acceptability of OP compared to conventional conservative management (usual care) of women with moderate or severe OHSS? We hypothesise that the use of OP in the management of moderate or severe OHSS will result in earlier resolution of symptoms and avoid the need for hospital admission, when compared with usual care.

3. Aims and objectives

3.1 Aims

The study aims to establish the clinical and cost-effectiveness, safety, and acceptability of OP as an active management for women with moderate or severe OHSS, in a multi-centre adaptive RCT with internal pilot to assess the feasibility of conducting the RCT.

3.2 Objectives

The primary objective is to establish whether OP reduces the rate of OHSS related hospital admissions in those presenting with moderate or severe OHSS compared to usual care.

Secondary objectives are to:

1. Establish whether OP prevents the escalation of OHSS severity compared to usual care
2. Establish whether OP reduces the time taken for OHSS symptoms to resolve compared to usual care
3. Establish the safety of OP as an active intervention for moderate or severe OHSS compared to usual care
4. Explore whether OP would improve patient satisfaction and quality of life of participants compared to usual care
5. Establish whether OP is cost-effective compared with usual care by examining healthcare resource use and patient costs
6. Facilitate the feasibility of conducting the RCT by identifying problems with the conduct of the RCT during the internal pilot, so that solutions can be instigated.

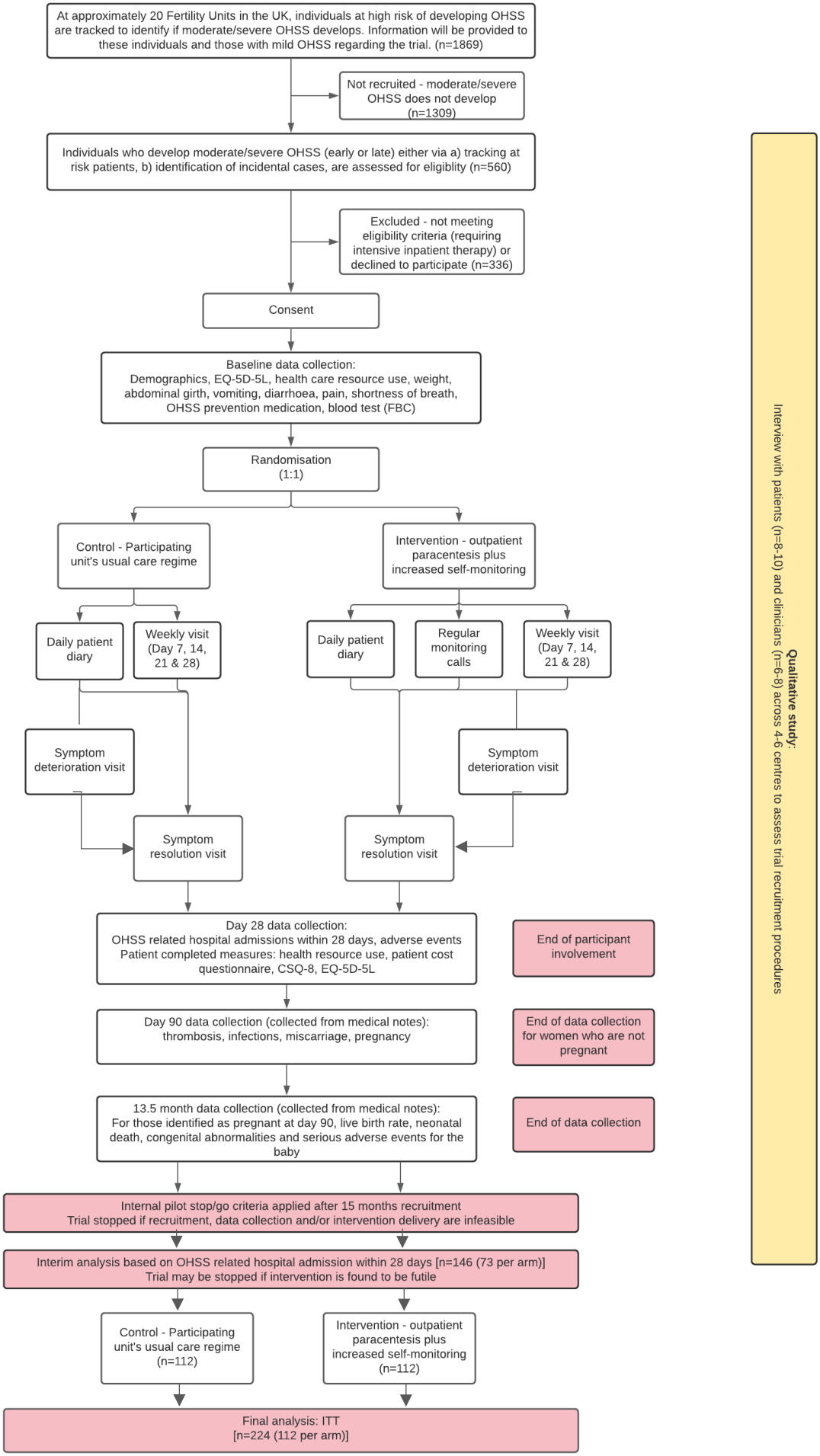
4. Trial Design

STOP-OHSS is a pragmatic, parallel open-label, multi-centre, superiority, adaptive, group sequential, confirmatory RCT with an internal pilot to assess feasibility aspects (Figure 1). Participants will be individually allocated 1:1 to receive conservative management or OP.

A qualitative study will be conducted during the internal pilot phase to facilitate the feasibility of conducting the RCT by identifying problems so that solutions can be instigated rapidly.

A total of 224 women with moderate to severe OHSS will be randomised to the trial - a 0% withdrawal rate is assumed as the primary outcome is short term, occurring at 28 days from randomisation, and can be collected directly from patient notes with informed consent. About 20 private and NHS Fertility Units are expected to take part from England and Scotland. The trial will last approximately 32-months.

Figure 1 STOP-OHSS Trial Flow Chart



4.1 Internal pilot phase

To address secondary objective 6 (Section 3.2), a 15 month internal pilot will follow the recommendations of Avery et al (23) to assess feasibility aspects relating to rates of recruitment, retention of randomised participants and intervention delivery. The completion of the trial is contingent on meeting progression criteria described in section 8.2.4. Qualitative research will be conducted within the internal pilot phase in order to identify problems with the conduct of the RCT, see Section 12.

5. Selection of participants

This section covers the trial population, eligibility criteria, participant identification, consent process, screening procedures, and any other criteria that will affect participation in the study including co-enrolment.

The trial population will be women undergoing ARTs (including IVF and IUI) who experience moderate or severe, early or late OHSS symptoms, as defined in Section 2.1.

The women will be treated in either NHS or private fertility units in England and Scotland. There has been an increase in the number of privately funded IVF cycles (1) that occur in private and not NHS units, however, the burden of OHSS when it occurs in private units can be picked up by the NHS. It is therefore important to engage with and involve private units in addition to the NHS fertility units.

5.1 Eligibility criteria

Eligibility criteria are designed to be pragmatic and inclusive by only excluding women who could not be randomised to the intervention arm for safety reasons or who are unable to follow the study protocol.

5.1.1 Inclusion criteria

1. Women presenting with moderate or severe, early or late OHSS as defined in Section 2.1
2. Patients able and willing to attend weekly follow-up appointments in person or remotely, daily remote appointments/phone calls, and able to undertake self-monitoring at home.

5.1.2 Exclusion criteria

1. OHSS-related exclusion criteria:
    a. Significant pain* or vomiting requiring hospitalisation;
    b. Pulmonary embolism;
    c. When in the judgment of the clinician, the patient's condition is severe enough to warrant admission to a High Dependency Care Unit (such as Critical OHSS as defined in the Royal College of Obstetricians and Gynaecologists (RCOG) green-top guidelines) and therefore not suitable for outpatient management.
2. Non-OHSS related medical conditions: A concurrent medical condition requiring immediate inpatient management.

3. Patients who have been previously randomised but later present with moderate or severe OHSS symptoms in subsequent cycles after their initial trial involvement
4. Participation in other trials involving ovarian stimulation or ovarian response

*Significant pain will require clinical judgement but may be guided by whether the patient is able to manage the pain at home using 'over the counter' analgesia or if there are any clinical concerns regarding other conditions potentially contributing to the pain (e.g., ectopic pregnancy).

5.2 Participant identification

Women will be identified via two methods:

1) Monitoring – women considered at risk of developing moderate or severe OHSS who are regularly monitored as part of their usual care will be identified, informed about the research and provided with brief information about the trial. The local nurse or clinician could consider monitoring notes for women with the following medical histories for potential trial enrolment as these indicate that the patient may develop OHSS:

Early OHSS

- Women attending for egg collection with >15 eggs who may or may not be symptomatic of OHSS
- Women who are symptomatic of OHSS bloating/nausea etc and are being observed remotely or in person at clinic for clinical review and requiring scans/bloods (FBC) etc
- Women, who have shown a high response to stimulation with increased follicular activity
- Younger women (i.e., <30yrs) who have a good ovarian reserve and are therefore known to respond well to treatment
- Women suffering with Polycystic ovary syndrome
- Women with a low BMI
- Women who have experienced OHSS in previous cycles but have not previously been randomised into this study
- High levels of Anti-Müllerian hormone (greater than 30 pmol/l)

Late OHSS

- Women who contact or are contacted by the unit post embryo transfer with symptoms of OHSS (i.e., breathlessness, bloating, or nausea)
- Women monitored in the early phase as documented above and who may also go on to have late onset OHSS

The above lists are not exhaustive, but will act as a guide to be used along with the clinical judgement of local site staff.

Women who already have mild OHSS and are presenting with symptoms of OHSS, for example bloating, breathlessness or nausea, should also be monitored. These women should be monitored for progression to moderate or severe OHSS using existing local procedures and full written informed consent requested if they progress to moderate

or severe OHSS. Local site staff will be asked to record anonymised details of patients being monitored.

A brief participant information sheet and/or details of a short film introducing the study should be provided to potential participants being monitored, for example, at one of the following timepoints:

- When the woman is starting injections;
- When the follicles start growing;
- When the woman first informs or has contact with the fertility unit about symptoms of mild OHSS.

It is advised that local centres wait until after the potential participant has started the IVF process before making the initial introduction about the study due to the amount of information provided to the women initially.

Posters may be placed within the fertility centre to raise awareness of the study.

2) Incident cases – patients with moderate or severe OHSS presenting at fertility units not previously identified as at risk may also be approached and recruited, providing there is enough time for the woman to understand the nature of the study and provide written informed consent.

For both methods detailed above, monitoring of cases who would normally be monitored through usual care processes and incident cases allow a pragmatic approach to recruitment.

5.3 Eligibility screening

Screening will take place when either the woman presents with, or those being monitored progress to, moderate or severe OHSS. Assuming a 40% consent rate we anticipate screening approximately 560 patients. After screening failures, enrolment of 224 participants is expected (see Section 11.1).

The assessment of eligibility will be undertaken by the principal investigator (PI) or another suitably qualified member of the research team, who has received appropriate training and has been approved by the PI as detailed on the delegation of responsibilities log.

Eligibility assessment will be based on medical notes and routine clinical investigations already undertaken to confirm the diagnosis of moderate or severe OHSS, and will include ultrasound scans to confirm the presence of ascites.

5.4 Informed consent

Eligibility will be confirmed and consent will be obtained by the site PI or other appropriately trained member of the site research team and/or the central research nursing team who has been delegated to conduct this activity.

Potentially eligible participants should be approached in relation to consent as soon as possible after the diagnosis of moderate or severe OHSS is made and, where possible, initial eligibility screening has taken place. To facilitate this site staff should provide the patient with the participant information sheet and/or the link to the animation film outlining the study during the clinical appointment arranged to investigate the patient's moderate or severe OHSS symptoms.

5.4.1 Informed consent process

Women may be told about the study initially by a member of the local research team and written consent will then take place in clinic due to the urgent nature of the condition. Women will be able to consent, have their baseline checks and be randomised during the same visit wherever possible and provided with the trial treatment (if applicable) as soon as possible thereafter. It is acknowledged that in some cases - either because the woman may need more time to consider their involvement or for practical reasons - they may need to come back one or two days later, but any delay should be minimised where possible. Women may also be given the option to receive further information from a member of the central research nursing team, based at the Jessop wing -Sheffield Teaching Hospitals NHSFT. If this option is pursued, the woman will be asked to give verbal consent for their contact details to be given to a member of the central research nursing team (consent to contact) only once the PI has confirmed trial eligibility. The local sites will be required to identify, assess eligibility, and make a first initial approach to enquire whether the patient might be interested in taking part in the STOP-OHSS trial. A member of the central research nursing team may then take patient consent, conduct randomisation and enter data onto the Prospect system on behalf of the local research site.

Consent Process if the centralised team take consent

It is expected that for the majority of recruitment, the local research team will take patient consent. However, in the case of situations where the local research team require support from the central research nursing team the process will be;

- Local research team will approach the potential participant and ask the participant to give verbal consent for their contact details to be given to a member of the central nursing team.
- A member of the central nursing team will then take the patient consent and randomise the patient.
- An automatic electronic email confirmation is sent to designated members of the local research team, the study manager and the central nursing team to confirm randomisation.
- The central nursing team will then confirm with the local site research team that the process has taken place.

The woman should be allowed as much time as needed to consider their participation. The potential participants should be informed about the potential risks and benefits of the trial, have the opportunity to discuss the trial with family/friends etc and be able ask questions with a suitably trained and qualified member of her clinical or research team.

Participation is entirely voluntary and choosing not to participate will not negatively influence the woman's treatment in any way. The right of the patient to refuse consent without giving reasons will be respected. Furthermore, the participant will remain free to withdraw from the study at any time without prejudicing any further treatment.

Consent should be considered as part of an on-going dialogue with the participant and should be re-confirmed at each visit and study procedure.

A record of the consent process detailing the date of consent and all those present will be recorded in the participants' hospital notes. The original consent form will be filed in the investigator site file, a copy retained in the hospital notes and a second copy will be given to the participants. If the central research nursing team obtain consent,

perform randomisation etc. then a written record of the discussion and proocedure will be performed and sent to the local research site for filing in the participants medical notes for the purposes of source data. This information will be sent via nhs.net

Following consent, the participant's details will be recorded and entered on to the trial database. If consent is refused or if the patient is not eligible then the reasons for refusal/ineligibility will be requested (but they do not have to provide this if they do not wish to do so), and basic information will be recorded to enable completion of the Consolidated Standards of Reporting Trials (CONSORT) diagram to enhance the interpretation of trial results.

5.5 Co-enrolment guidelines

Potential participants should not be enrolled if they are taking part in another trial involving ovarian stimulation or ovarian response. If local sites are uncertain about whether studies meet this criterion they should contact the Trial Manager/Lead Research Nurse or CI.

6. Trial treatment

The intervention is OP with increased patient monitoring. This will be referred to as OP throughout the protocol.

OP involves drainage of ascitic fluid either vaginally or abdominally depending on experience of local clinical staff and patient symptoms. Patients will also receive increased monitoring during which clinicians will review clinical indicators and make contact with the patient at regular intervals (initially daily) (see Section 6.1.2).

6.1 Patients randomised to outpatient paracentesis

Participants randomised to the OP arm will be invited to attend an outpatient appointment to have their abdominal fluid drained. The timing of the paracentesis procedure following randomisation for each participant is at the discretion of the local investigator; however, they should aim to complete the procedure as soon as clinically possible.

The route of paracentesis (abdominal/ vaginal) will be based on clinician preference and resources available. The procedure will:

- take place in an outpatient location with an ultrasound machine (e.g., fertility unit, gynaecology unit, radiology etc) as per the site's preference.
- be undertaken by an appropriately trained and qualified healthcare professional (e.g., Doctor, Advanced Nurse Practitioner, Radiologist)

There will be a pragmatic approach to intervention delivery by allowing sites to follow their local procedures for conducting paracentesis, however we have provided some general procedural information below to assist with this.

6.1.1 Procedural Information

General procedural information

1. The procedure should be conducted under ultrasound guidance.
2. Appropriate pain relief should be given,

3. No maximum fluid drainage.
    a. Amount drained and length of procedure will be recorded.
    b. The procedure will continue until ultrasound examination shows the pelvic fluid is maximally drained based on clinical judgement.
4. Intravenous medications should be administered as required based on the participant's clinical status.
5. Rehydration
    a. Participants should undergo rehydration before and after paracentesis
    b. Intravenous colloid therapy should be considered for participants who have large volumes of fluid removed
    c. Participants kept in the hospital overnight (or for less than 24 hours) for rehydration will not be viewed as meeting the trial's primary outcome relating to hospitalisation

Transvaginal paracentesis

1. The vagina should be cleaned with an appropriate solution
2. The needle to be used is usually the type used for egg collection. Other equipment used may vary across centres
3. The egg retrieval needle fixed to a vaginal ultrasound probe, attached to conventional tubing and connected to suction
4. Suction applied
5. The egg retrieval needle should be directed into the posterior cul-de-sac, into the largest accessible pocket of fluid
6. The needle should be withdrawn slightly to avoid damage to surrounding organs at the end of the procedure
7. Suction activated and ascites fluid drained
8. Sterile flasks or canisters should be attached to the fluid collection port of the aspiration needle and emptied manually into a 1 litre measuring container.

Abdominal paracentesis

Transabdominal catheters e.g pigtail may be placed for continuous/intermittent drainage of ascites.

Some patients may need multiple drainages either abdominally or vaginally. These will need to be undertaken each time a participant has a re-accumulation of ascites fluid. The need to conduct multiple drainages will be based on clinical judgement.

The volume of ascites removed and number of paracentesis performed should be recorded.

6.1.2 Self-monitoring

Participants on the intervention arm will be asked to record self-monitoring information daily. Participants will be provided with a daily diary (in either paper form or electronic via a link to REDcap but be asked to record data in one or the other formats and not in both or a mixture of both to prevent double data entry and errors in confirming which is correct if errors are identified) to record this information and will be asked to report this during monitoring contacts which will initially take place daily but may then reduce based on clinical need.
NOTE: Women randomised to the conservative management group will still perform self-monitoring but this data will be sent directly to CTRU for input into the database and will not be reviewed by site staff.

6.1.3 Stopping treatment

Participants or clinicians may choose to stop trial-related treatment at any time and this will be recorded on the electronic Case Report Form (eCRF. Participants stopping trial treatment will revert to usual care at that site, but will continue in the trial and complete all other trial procedures, unless the participant requests trial withdrawal.

6.2 Patients randomised to conservative management (usual care)

The control group will be conservative management, which at most sites is usual care. Conservative management may differ from clinic to clinic and may be dependent on whether the OHSS is classed as moderate or severe, early or late. If usual care at the site involves administering paracentesis on an outpatient basis for treatment of OHSS then the site will be requested to stop routinely providing this for participants in the conservative management arm. Details of the usual care received will be collected.

The research/clinic nurses/research staff will monitor the control group as per usual practice at that site. Control group participants will be provided with a patient diary (paper or electronic) to record their daily symptoms which is not currently part of usual care and will therefore make the trial less pragmatic, however this information will be collected for the purposes of research outcomes only and will not be monitored clinically, unless this is part of usual care at that centre.

Some fertility units undertake other preventative measures (e.g., dopamine agonists, GnRH antagonists, cessation of IVF cycle) in order to reduce the risk of OHSS - whether these measures have been taken, what they are and when the measure was taken will be collected during the trial, along with information on the provision of care within the conservative management arm.

Rarely, patients may be prescribed GnRH antagonists as treatment for established moderate or severe OHSS. This will not be prohibited for trial participants in both arms and data will be collected on GnRH use within the trial.

7. Randomisation, allocation concealment, and enrolment

Eligible and consenting patients will be randomised using a centralised web-based randomisation system (SCRAM) hosted by Sheffield CTRU. This system has user-restricted functionalities that grant access rights to specific areas that are appropriate depending on the roles in the trial.

Participants will be randomly allocated (1:1) to receive either usual care or early OP (as described in Section 6) using stratified permuted block randomisation stratified by recruiting site and severity of OHSS (moderate or severe). Block sizes will be disclosed during dissemination of findings and only the randomisation (trial) statistician who is not involved in the recruitment process will know the block sizes during the trial. The trial statistician will log on to the system and generate the randomisation sequence that will be retained within the system; however, they will not have access to the generated sequence.

Following informed consent, delegated research staff at sites or the central research nursing team will log on to the SCRAM system and enter details to confirm their eligibility and consent as well as the recruitment site, and severity of their OHSS (moderate or severe). At the request of the randomising research staff, the details are then submitted, and the allocated treatment arm will be displayed on a computer screen. The participant will be informed of their allocation, and if allocated to the OP arm arrangements will be initiated for the procedure to take place. The designated Sheffield CTRU statistician independent of the day-to-day conduct of this trial and tasked to perform interim analysis will have access to the allocation sequence.

Finally, it should be noted that participants who have been previously randomised but later present with moderate or severe OHSS symptoms in subsequent cycles after their initial trial involvement will not be eligible for re-randomisation into the trial.

7.1 Blinding

The trial will be open-label as it will not be possible to blind participants, investigators, nurses or other clinicians to the treatment allocation due to the nature of the intervention.

To assess the potential impact of outcome assessment bias, an additional analysis of the primary endpoint will be performed, using an independent blinded adjudicated primary outcome concerning whether trial participants needed hospitalisation within 28 days from randomisation (see Section 8.2.1).

The trial statistician(s) will have no access to unblinded data during the conduct of the trial and will be unblinded only for the final analysis. The responsibility to conduct interim analyses will be delegated to a Sheffield CTRU trial statistician who is independent of the day-to-day conduct of this trial.

The trial health economists will not have access to unblinded data until the interim analysis timepoint when they will conduct interim health economic analyses on unblinded data. This decision has been made to balance the practicalities of this interim analysis, the benefits of blinding and the risks of unblinding the health economist during the trial. Practicalities include, a suitable alternative health economist with experience in adaptive design will not be identified, benefits include that an expert presents the data to the Data Monitoring and Ethics Committee (DMEC) and the risks include influencing the future conduct of the trial. Practical steps will be taken to mitigate any risk of bias after the interim analysis, including that:

- Health economists will not discuss interim trial results with unblinded team members and will continue to attend the Trial Management Group (TMG) but will focus on their role of ensuring health economics data are collected,
- The unblinded statistician designated to conduct the interim analysis will be the point of contact to discuss concerns with if required.

Members of the Trial Steering Committee (TSC) will be blinded to treatment allocation throughout the trial. The TMG will receive blinded data reports, however, members of the TMG, including the CI, based at Sheffield Teaching Hospitals (STH) and Sheffield CTRU will need to be unblind to individual participant's allocations in order to coordinate the trial and deal with adverse events (AEs) and other medical emergencies.

Individuals on the TMG will be blinded to treatment allocation when making assessments in relation to the secondary outcomes of the need for hospitalisation and the time to resolution of symptoms.

Procedures outlined in Sheffield CTRU standard operating procedure (SOP) ST009 on Blinding will be followed.

7.2 Unblinding

The statistical analysis plan (SAP) and heath economics analysis plan (HEAP) will be developed and signed off before accessing unblinded data. As described in Section 7.1, health economists will be unblinded during interim analysis. Unblinding of trial statisticians will not take place until the statistical analysis plans are approved and at the point of data freeze (when general write access to the study database is revoked and the data released to the statistician for review). The DMEC will have access to unblinded data during the closed session of the DMEC meetings. The CTRU data management team will have access to unblind data and will produce the reports for the DMEC and those conducting unblind analyses.

8. Outcomes

All outcome time-points will be measured post-randomisation, unless stated otherwise.

8.1 Primary outcome

The primary outcome will be any OHSS related hospital admission of at least 24 hours (primary objective Section 3.2), within 28 days of randomisation. This data, including reasons for hospitalisation, will be collected by staff at fertility units contacting the participant by telephone during monitoring, at patient visits (e.g., symptom deterioration visit), or collected from hospital notes after 28 days.

Participants admitted for short periods (less than 24 hours) for various reasons such as immediate rehydration, pain relief administration etc., will not be considered as a failure of treatment.

Sites should use clinical discretion on decisions to hospitalise a participant, and keep in mind the GTG 5 OHSS Green-top guidance on the management of OHSS 2016 (1) or any updated guidance that the RCOG publishes during the course of the trial.

To avoid potential bias in assessing the primary outcome because of the open-label nature of the trial an adjudicated, blinded central assessment will take place as a secondary outcome (see Section 8.2.1).

There may be a delay to the start of treatment for some patients in the intervention group. We chose the primary outcome to be assessed from randomisation rather than the start date of treatment for two reasons; first, to ensure that the follow-up

period is the same across treatment arms to reduce potential biases. Second, the OP treatment strategy is aimed at intervening early, so it is expected to be offered to participating women as soon as possible after randomisation. Potential delays in treatment (e.g., because it cannot be offered on a weekend) are inherent in the treatment strategy and should be reflected in the outcomes, in line with the pragmatic nature of the trial. This will allow us to estimate the effect of OP when used in real-world setting where treatment delays will be expected to occur even if the treatment strategy is intended as an early intervention.

8.2 Secondary outcomes

The trial will assess the following secondary endpoints relating to clinical efficacy, health economics evaluation, safety, and internal pilot objectives defined in Section 3.2.

8.2.1 Efficacy

Adjudicated need for hospitalisation within 28 days – independent blinded central assessment

Potential biases may arise in decisions to hospitalise because of the open-label nature of the trial. To aid interpretation of the primary outcome results, an independent blinded central assessment of the OHSS-related need for hospitalisation of at least 24 hours within 28 days post-randomisation will be conducted. This will allow the study team to assess the potential impact of any unblinded outcome assessment bias in relation to the primary outcome (primary objective Section 3.2).

The criteria used for central assessment will be based on green top guidance and identification of current practice across centres. The criteria will be held in a separate controlled document.

Clinical members of the TMG will conduct a blinded assessment - without access to personal data, identifiers or site information - regularly throughout the trial. The assessment will be informed by data collected during symptom deterioration visits or other routes of hospitalisation, including clinical data and reasons stated for hospitalisation.

Cumulative length of OHSS related hospitalisation

In addition to the binary primary outcome, we will also record total cumulative length of OHSS related hospital admission, providing a measure of the total burden of hospital stay assessed within 28 days post-randomisation to provide supplementary information feeding into resource use and patient costs (secondary objective 5 Section 3.2). This will include any admissions for short periods that may not have met the primary outcome.

Time to symptom resolution

To address secondary objective 2 the time to symptom resolution within 28 days post-randomisation will be measured. Confirmation of symptom resolution will be measured by **all** of the following things happening together:

1) normalisation of the haematocrit and haemoglobin concentrations
2) normalisation of fluid input and output (no longer in a positive fluid balance)
3) decrease in weight
4) decrease in abdominal girth

The participant may not be completely asymptomatic of OHSS as complete resolution of symptoms may take a significant amount of time, but will meet the criteria outlined above.

This outcome will be informed by daily patient diaries and in-clinic visits, in particular the symptom resolution visit. The symptom resolution visit will be triggered by an indication that daily symptoms have resolved, defined by items 2 to 4 in the above criteria being present from participant self-report. Participants will be requested to complete daily patient diaries up until the symptom resolution visit to assist with collecting data for this outcome measure. The patient diary will include a fluid balance chart for the women to include daily oral intake and urine output and will also record other symptoms such as vomiting and diarrhoea. Participants will be provided with tape measures and weighing scales to measure abdominal girth and weight. Blood tests and other investigations will be undertaken during in-clinic visits as appropriate.

Time to resolution of OHSS will be based on the criteria above and, due to potential delays in the timing of symptom resolution visits and differences in the frequency of monitoring between the groups, will use a combination of patient diary data and clinical data from this visit in order to determine the timing of symptom resolution – the assessment will be made centrally, blinded to treatment allocation. This assessment will reduce the risk of bias that may occur due to differences in monitoring frequency between the groups.

Progression of OHSS severity

Progression of OHSS severity (within 28 days post-randomisation, using trial definitions based on the RCOG guideline (1), see Section 2.1 will be informed by data collected at clinic visits and will inform secondary objective 1.

Progression criteria from moderate to severe

Indicated by fluid accumulation in abdomen which becomes clinical ascites/clinically detectable with or with hydrothorax, with any of the following additional symptoms:

- Clinical ascites (± hydrothorax)
- Oliguria (< 300 ml/day or < 30 ml/hour)
- Haematocrit > 0.45
- Hyponatraemia (sodium < 135 mmol/l)
- Hypo-osmolality (osmolality < 282 mOsm/kg)
- Hyperkalaemia (potassium > 5 mmol/l)
- Hypoproteinaemia (serum albumin < 35 g/l)
- Ovarian size usually > 12 cm

Progression criteria from severe to critical

Indicated by evidence of any one of the following features:

- Participant has a large hydrothorax
- Increasing haematocrit levels to >0.55
- A white cell count of over 25000/ml (confirmed via– FBC test)
- Change from Oliguria (low urine output) to Anuria (very little/no urine) (< 100 ml/day)
- Thromboembolism
- Acute respiratory distress syndrome

Progression from moderate to critical will also be collected using the progression criteria above.

Patient Satisfaction

Patient satisfaction with their care will be measured at 28 days post-randomisation, using the Client Satisfaction Questionnaire 8 (CSQ-8) (24). This is an eight-item questionnaire, where questions are scored on a scale of 1 (low satisfaction) to 4 (high satisfaction), resulting in total scores of 8 to 32. The validity and reliability of this survey has been demonstrated across varied service settings (25).

8.2.2 Health economics

EQ-5D-5L participant quality of life

EuroQoL-5D-5L: The EQ-5D is a routinely used generic health related quality of life (HRQL) instrument. It is the preferred instrument for assessing HRQL by The National Institute for Health and Care Excellence (NICE), and the five-level (EQ-5D-5L) instrument offers increased sensitivity as opposed to the original three-level version.(26) EQ-5D-5L will be measured daily by self-report in patient diaries until symptom resolution and then at 28 days post randomisation.

Health resource use and patient costs

Resource use by participants will be measured using a resource use questionnaire (at 28 days post randomisation). Resource use will not be collected at baseline as patients are likely to be quite sick at this point and we envisage they would either be unable to complete or unable to complete reliably the resource use measure. A modified version of the Client Service Receipt Inventory (CSRI) (27) will be used. The CSRI is a routinely used instrument to capture health resource use and personal expenses.

Patient costs will be collected using a trial specific version of a patient cost questionnaire to ask for cost information relating to the participant's most recent visit to the clinic (at 28 days post-randomisation).

Further resource use data will be collected during the trial to inform the health economics analysis, on areas including training of staff and participants on the trial and consumables given; details of monitoring given to participants; outpatient treatment delivery details; hospital admission information; and treatment received. Full resource data requirements will be specified in a HEAP.

8.2.3 Safety outcomes

Thrombosis or embolism

The occurrence of thrombosis or embolism observed within 90 days post randomisation will be collected from the participant's medical notes and whether they were hospitalised as a result.

Infections

The occurrence of significant infections requiring antibiotic treatment or hospitalisation within 90 days post randomisation will be collected from the participant's medical notes and whether they were hospitalised as a result.

Live birth, pregnancy outcomes, neonatal death, and serious adverse events in the new-born

Live birth, pregnancy outcomes (e.g., miscarriage), neonatal death, and serious adverse events including congenital abnormalities in the new-born, up to 6 weeks post-partum will be collected from medical notes (at 13.5 months post-randomisation).

For participants recruited in the final 12.5 months of the recruitment phase of the trial, an "ongoing pregnancy" rate will be collected, as the live birth event is likely to occur after the end of the follow up period of the trial.

Other Adverse Events

The frequency and type of AEs will be collected and presented. Data collected which inform other outcome measures such as nausea, shortness of breath or OHSS related hospitalisation will not be reported as separate safety outcomes. See section 10 for details. All participants will be asked about any AEs at 28 days post-randomisation and medical notes reviewed to ensure that no events have been missed previously and will aim to avoid bias due to the difference in monitoring between the two treatment groups at which AEs may be identified.

8.2.4 Stop/Go Assessment

We have followed the recommendations of Avery *et al.,* in setting green/amber/red progression criteria(23).
We will assess the following feasibility outcomes at 15 months of the recruitment window:

1) Participant recruitment (both arms),
2) Retention of randomised participants (both arms),
3) Delivery of the OP treatment (only OP arm).

The TSC will make a recommendation to the NIHR using the following criteria, where green indicates continuation of the trial, any amber indicates that steps should be in place to regain ground and any red indicates the trial is not feasible, as summarised in Table 1. Targets will be assessed following 15 months of a 31-month recruitment window.

Table 1. Progression criteria for internal pilot feasibility assessment

Domain	Target at 15m	Green	Amber	Red
Participant recruitment	An average of 4.6 participants per centre per year (0.38 per month) or 96 in total	A minimum 75% of total target*.	50-<75% of total target*.	Below 50% of total target*.
Participant retention	100% of randomised participants at 28 days with primary outcome data	A minimum 95% of target.	80-<95% of target.	Below 80% of target.
Intervention delivery	100% of women randomised to the intervention arm	A minimum 90% of target.	70-90% of target.	Below 70% of target.

	receive outpatient paracentesis procedure within 5 days of randomisation.			

* If the total target is not met but the per centre per month (0.38) figure is on target then the trial team will need to demonstrate a clear plan and timescale for opening futher open sites

9. Assessments and procedures

Ideally during one initial visit potential participants will

- have their eligibility assessed,
- will be asked to provide informed consent,
- have baseline measures and blood tests,
- be randomised onto the study,
- trained in any trial-related procedures, including completion of the patient daily diary
- be provided with consumables and any questionnaires or paperwork relating to the study,
- if randomised onto the outpatient paracentesis arm, arrangements made for procedure to be conducted

Day 0 is the date of randomisation into the study.

There are several visits that participants from both arms of the trial will be asked to attend:

- Outpatient monitoring visits at days 7, 14, 21 and 28 or until symptoms have resolved
- A symptom resolution visit when the symptoms are resolving (unless symptoms resolve during hospitalisation and the data can be collected from medical notes or from the participant)
- A symptom deterioration visit to assess if hospitalisation may be required.

Monitoring visits may take place face-to-face in clinics or via remote methods. If there is any concern identified for the participant, then they must be invited to a face-to-face appointment. Scheduled visits should normally be as close as possible to the scheduled visit date for safety reasons. However, where this is difficult to arrange, e.g. due to Bank Holidays or participant availability, participants should attend as soon as possible after that date. For full details of study assessments, see Section 9.1 below.

9.1 Study assessments schedule

Data will be collected at the time points listed below. Follow-up time points should be measured from the date of randomisation.

9.1.1 Baseline

Baseline data collection will include:

Participant reported data

- demographics and contact preferences
- EQ-5D-5L
- height
- weight
- size of abdomen
- whether they suffered from diarrhoea in the past day
- whether they have been sick or not in the past day (amounts are not needed) and how many times they have been sick.
- pain experienced for safety reasons, using NRS scale to rate average pain experienced over last 24 hours from 0-10.
- Asking about shortness of breath for safety reasons, in case of pulmonary embolism

Data from medical records
Data needed from the notes will include whether they were on medication to prevent OHSS, for example GnRH or cabergoline

Assessments
If not conducted in the previous 24 hours - Initial blood tests x 2 for FBC (for haematocrit and white blood cell count).

9.1.2 Daily Patient Diary

All participants will be asked to complete a daily diary of their symptoms. This will include:

- Weight
- Abdominal girth
- Diahrrhoea in the past 24 hours
- Vomiting in the past 24 hours
- Pain
- Shortness of breath
- Fluid input
- Urine output

Sheffield CTRU will send participants daily texts reminding them to complete the patient diary.

9.1.3 Weekly until symptom resolution (day 7, 14, 21 & 28-/+ 2days)

All participants will be asked to attend weekly outpatient appointments (day 7, 14, 21, & 28), either in clinic or via remote appointment up to day 28 or until their symptoms have resolved. There will be a visit window of -/+ 2 days for each appointment time point.

If the participant has been hospitalised then these visits will not be required and the data will be collected from the participant's medical notes or by contacting the participant directly. The primary purpose of weekly monitoring visits is for safety, so if they are in hospital we will not need to complete additional monitoring.

At these visits, the research/clinic nurse/researcher will collect the following data:

- Fluid input/ output (including nausea, vomiting & diarrhoea)

- Abdominal girth
- Weight
- Pain
- Shortness of breath
- Blood samples (FBC) if a face-to-face appointment
- Adverse events (including hospital admissions)
- Whether prescribed GnRH antagonist as treatment, and if applicable, details on when it was given, dose and schedule will be collected

The research/clinic nurse/researcher will ask for the return of the completed patient diaries (if a face-to-face appointment) and will provide or send extra copies if needed.

For participants who have received paracentesis they will also document the volume of ascites removed and number of paracentesis performed.

If appropriate, A member of the central research nursing team may also contact the participant to collect this data, if the participant has consented to this and again a record of the visit will be documented and returned to the local research site for filing in the participants medical records via nhs.net.

9.1.4 Symptom resolution

Once regular monitoring indicates that symptoms have resolved as defined in section 8.2.1, the participant will be asked to attend the clinic to confirm this. The research/clinic nurse/researcher will collect the following data:

- Fluid input/ output (including nausea, vomiting & diarrhoea)
- Abdominal girth
- Weight
- Pain
- Shortness of breath
- Blood samples (FBC)
- Adverse events
- Confirmation of symptom resolution form
- Any OHSS related hospital admission within 28 days
- Whether prescribed GnRH antagonist as treatment, and if applicable, details on when it was given, dose and schedule will be collected

For participants who have received paracentesis, data will be collected on the volume of ascites removed and number of paracentesis performed (if not already collected)

9.1.5 Symptom deterioration

Participants whose symptoms have deteriorated will be asked to attend the clinic for an outpatient visit.

The research/clinic nurse/researcher will collect the following data:

- Fluid input/ output (including nausea, vomiting & diarrhoea)
- Abdominal girth
- Weight
- Pain
- Shortness of breath

- Blood samples (FBC)
- Adverse events
- Whether prescribed GnRH antagonist as treatment

At this visit, the research / clinical team will determine if the participant should be hospitalised and record reasons for this.

9.1.6 During hospitalisation

Sites will be asked to follow their usual clinical procedures and GTG 5 OHSS Greentop guidance (1) on the management of OHSS 2016, or any updated guidance that the RCOG publishes during the course of the trial, to determine if a participant should be hospitalised.

We wish to continue to collect the following types of data during hospitalisation daily from the participant directly or their medical records:

- Fluid input/ output (including nausea, vomiting & diarrhoea)
- Abdominal girth
- Weight
- Pain
- Shortness of breath

We will ask the research/clinic nurses/researcher to collect the following information about hospitalisation from the participant's medical notes:

- Blood test results (FBC)
- AEs
- Location and duration of admission
- Interventions received (including timing)
- Confirmation of symptom resolution form (if applicable)
- Whether prescribed GnRH antagonist as treatment
- Other treatment given

Collection of hospitalisation data may involve the research/clinic nurse/researcher contacting or travelling to other hospitals.

9.1.7 Follow-up at Day 28

Research/clinic nurses/researcher will record any OHSS-related hospital admissions within 28 days (including reason for admission). Data will be collected via medical notes or by contacting the participant directly to request the information.

Sheffield CTRU will send the following questionnaires to the participant:

- Health resource use questionnaire
- Patient cost questionnaire
- Client satisfaction questionnaire (CSQ-8)
- EQ-5D-5L
- Adverse Events

9.1.8 Follow up at Day 90 and 13.5 months

<u>Day 90</u>

Research/clinic nurses/researcher will review the participant's medical notes to collect data regarding thrombosis or embolism and significant infections requiring antibiotic treatment or hospitalisation. They will also check for evidence of an ongoing pregnancy and pregnancy outcome (e.g,. miscarriage). Participants who are not pregnant at the point of day 90 data collection will be considered complete and will not require further data collection at 13.5 months.

13.5 months

For those participants who were identified as pregnant at 90 days, research/clinic nurses/researcher will review participant's notes to collect live birth information, pregnancy outcome (e.g., miscarriage) as well as neonatal death, congenital abnormalities and SAEs for the baby.

This data will not be collected for participants recruited in the final 12.5 months of the trial recruitment period.

Table 2 - Data collection time points

	Baseline/ randomisation (Day 0)	Daily until symptom resolution	Weekly (Days 7, 14, 21, 28)	Symptom Resolution	Symptom Deterioration[#]	During hospitalisation	Day 28	Day 90	13.5 months
Data collected by site staff									
Demographics and medical history (including medication to prevent OHSS)	OPt								
Symptoms: - Fluid balance including fluid drunk, urine output* - Diarrhoea and vomiting - Nausea** - Abdominal girth - Pain - Shortness of breath - Weight	OPt	SR	T/OP[^]	OPt	OPt	IP / MN			
Blood tests (FBC) – if a face-to-face appointment	OPt		T/OP[^]	OPt	OPt	IP / MN			
Training and provision of consumables, and record details	OPt								
EQ-5D-5L	OPt	SR				SR / IP			
OHSS related hospital admission within 28 days (primary outcome) and reasons for hospitalisation			T/OPt	OPt	OPt				
Intervention delivery (volume of ascites removed, number of paracentesis)			MN	OPt		MN			
Conservative management arm – details of usual care monitoring			MN	OPt					
Use of GnRH antagonist for treatment of OHSS			OPt	OPt	OPt	IP / MN			
Confirmation of symptom resolution				OPt		MN			
Adverse events (patient)		T***	OPt	OPt	OPt	IP	Q		

Pregnancy outcome (e.g miscarriage) and ongoing pregnancies								MN	
Incidence of thrombosis or embolism or significant infection								MN	
Live birth information and pregnancy outcome (e.g. miscarriage)									MN
Neonatal death, and SAEs related to the baby									MN
Data collected by the central study team									
Health resource use questionnaire							Q		
Client Satisfaction Questionnaire (CSQ-8)							Q		
Patient cost questionnaire							Q		
EQ-5D-5L							Q		

OPt = Outpatient
IP = Inpatient
T = Data collected over the telephone by a research nurse
SR = Self-reported by the patient
MN = Medical notes

If symptoms deteriorate to the point where hospital admission is thought to be required
^ If OHSS symptoms have not resolved by this time point
Q = data collected via a questionnaire

* Fluid balance on day 0 will be SR.
**Nausea will not be collected at as part of the daily patient diary
***This will only be possible for participants who are being contacted daily. When they are not being contacted daily it will be asked at every contact

9.1.9 Central assessments post 28 days

The following outcomes will be completed by the central study team:

- Need for hospital admission (blinded)
- Progression of OHSS within 28 days (moderate to severe or critical and severe to critical) (blinded)
- Time to resolution (blinded)
- Cross-over of randomised women between treatment and control arms

9.2 End of self-reporting and monitoring period

It is anticipated that the majority of OHSS cases should have resolved by 28 days post-randomisation at which point self-reporting and monitoring for the trial purposes will stop. In the case that the OHSS has not resolved we ask that the sites revert to the clinical management of participants in both groups using usual care practices after trial completion after day 28.

9.3 Participant withdrawals

Participants may wish to stop study treatment, or there may be a clinical need to stop treatment – see -Section 6.1.3 for details. Participants randomised to the intervention arm, who withdraw from receiving the intervention will continue to be followed-up and will remain in the trial, unless they request to be withdrawn.

Participants may withdraw their consent for the trial at any time, without providing a reason for this. This will be documented on a study completion/ discontinuation form and in the patient medical notes. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent. Consent will be requested from withdrawing participants for the continued collection of routine data from their medical records.

Excessive participant withdrawal from treatment/follow-up has a negative impact on a trial. Centres will explain the importance of remaining on the trial to participants, and that changes to planned treatment need not imply withdrawal from the trial. Nevertheless, if participants do not wish to remain in the trial their decision must be respected. A related SOP within the Sheffield CTRU on participant discontinuation and withdrawal of consent (SSU003) will be followed.

9.4 Loss to follow-up

Participants will be defined as lost to follow up if data cannot be obtained (from either medical notes or participant self-report) confirming whether the participant has been hospitalised within the 28 day follow up period. If a participant is lost to follow up, this will be recorded in the eCRF using the study completion/discontinuation form. Routine data will continue to be collected from medical notes where available.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting AEs/reactions in clinical studies. These procedures are described in this section.

10.1 Definitions

Table 3: Adverse Event and Serious Adverse Event information

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant. (*refer to SOP PM0017 Adverse Events and Serious Adverse Events for non-CTIMPs more details*)
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected
Serious Adverse Event (SAE)	An adverse event which is serious, defined as any untoward medical occurrence or effect that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Is otherwise considered medically significant by the investigator ***
Related AE/SAE	An AE or SAE which is related to a research procedure

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission not caused by OHSS, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious AE/experience when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Identification

AEs and SAEs are defined as an event that occurs after the patient has provided written informed consent for trial entry and up to the completion of the Symptom Resolution visit or 28 day visit (whichever is latest).
Additional data collection points at 90 days and 13.5 months post randomisation will collect specified adverse events.

Participants will be asked for details of AEs weekly (day 7, 14 and 21) or until symptom resolution and then at day 28 post randomisation. AEs and SAEs may also be identified by the Research Nurse (local or central) , or any other individual, at any point during this time (e.g. from medical notes, during a follow-up, during contact with the participant, or during site monitoring). Specified AEs will be identified through review of medical notes at 90 days and 13.5 months post randomisation.

10.3 Recording and reporting

When an event is identified the process for recording and reporting outlined in Figure 2 will be followed. The Research Nurse, or any other member of site staff, should check the AE against the list of data for trial outcomes (see Table 3). If the AE is not a data item informing the trial outcome, the local PI (or other suitably trained member of research staff who has been delegated the task) should be notified immediately and will assess the event for classification as an SAE (see definition in section 10.1).

All AEs, other than those listed as trial outcomes will be recorded on the AE report form, within the participant eCRF, including those that fulfil the criteria for being serious (see Section 10.1). Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

Table 4 Trial outcomes and data items informing outcomes that do not require separate AE / SAE reporting

Outcomes up to 28 days post randomisation	Outcomes at 90 day data collection	Outcomes at 13.5 month data collection
Hospitalisation for OHSS	Thrombosis or embolism	Pregnancy outcomes, e.g., miscarriage, stillbirth, ectopic pregnancy
Progression of OHSS severity (moderate to severe, severe to critical, moderate to critical)	Significant infections requiring antibiotic treatment or hospitalisation	Neonatal death defined as the death of an infant within 28 days of life
Nausea		Pre-term delivery (before 37 weeks gestation)
Diarrhoea		Congenital abnormalities detected antenatally or postnatally*
Pain		Any other event relating to the baby that meets the definition of an SAE
Shortness of breath		
Fluid imbalance		
Increased haematocrit level		

* Congenital anomaly detected antenatally or postnatally [Common minor congenital anomalies as defined by the EUROCAT minor anomaly exclusion list will not be included as unexpected Serious Adverse Events. These excluded anomalies are either minor (e.g. skin tags), or expected for the gestation (e.g., patent ductus arteriosus in babies born <37 weeks)].

AEs

Any events meeting the definition of an AE, not listed in Table 4 above, will be recorded in the eCRF as an AE.

The central research team will categorise non-serious AEs against the list of expected AEs below.

Table 5 - Expected Adverse Events related to paracentesis

Procedure related (immediate)
• Lethargy
• Dizziness or light-headedness
• Increased pain in abdomen
• Bleeding from drainage site
• Skin condition as a result of leakage from drainage site
• Hypotension
• Haemorrhage/ laceration of major blood vessel
• Perforation or damage to internal organs

Serious Adverse Events
All AEs classed by the PI or delegate as serious will require more detailed information to be recorded in the participant CRF. In such cases, the event must also be reported to the Sheffield CTRU within one working day of the site becoming aware of the event (see Section 10.4).

Expected Serious Adverse Events

Expected SAEs are those events listed in Table 5 which are assessed as serious using the definition in Section 10.1.

Unexpected Serious Adverse Events

Any AE which meets the definition of serious but is not listed in Table 5 must be reported as an unexpected. CTRU will report all unexpected SAEs to the sponsor and DMEC. SAEs which are unexpected and related/ suspected to be related to the intervention will be reported further by the CTRU to the REC within 15 working days.

Causality
All SAEs will be assessed for causality or 'relationship to the intervention'. This assessment should be made by a trained clinician, usually the PI using the following classifications:

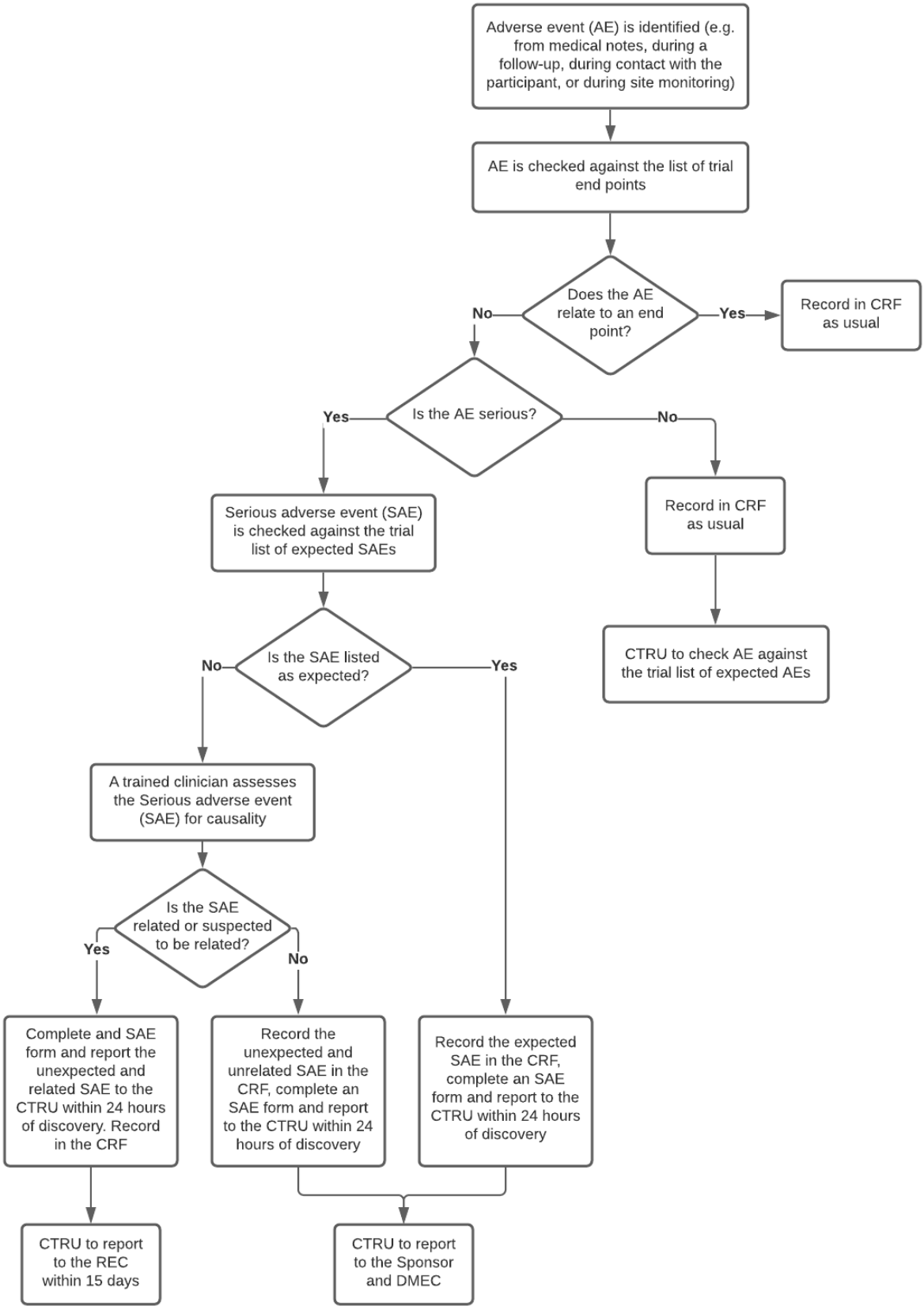
- Reasonable possibility of being related

- No reasonable possibility of being related
- Not assessable

If a causality assessment is not provided by the site or causality is recorded as ‘not assessable’, the CI should review and attempt to make an assessment. If the CI deems the event to be related and unexpected it will be reported to the Research ethics committee (REC) as per the ‘Additional reporting requirements for related, unexpected SAEs’ in line with the HRA Standard Operating Procedures for Research Ethics Committees. If the event is not assessable it will be discussed with oversight committees and monitored for further similar events.

Where there is disagreement between the PI and CI over the causality assessment the CI’s decision is final. Advice may be sought from the TSC if applicable.

Figure 2 AE and SAE reporting and recording



10.4 SAE recording and notification procedure

All SAEs (other than those which inform trial outcomes as detailed in Section 10.3) should be reported to the CTRU immediately and within one working day from the point of identification. Sites should enter a diagnosis into the reporting form. If a diagnosis is unknown at the time of submission to CTRU, the form may be updated at a later date.

SAE notification procedure

- Details will be recorded on an SAE form (filed in the Investigator site file or downloaded from the AE eCRF page) and sent to the Sheffield CTRU dedicated email address: ctru-saes-group@sheffield.ac.uk
  The email account will be checked during office hours (between 9am and 5pm Monday to Friday).
- Receipt of the initial report will be confirmed within one working day. Sites should contact the study team at CTRU if confirmation of receipt is not received within one working day.
- In the event that no clinical assessment can be made immediately, it is recommended that the SAE form is sent to the CTRU regardless, and an assessment is obtained as soon as feasible on a new SAE form and forwarded to the CTRU in Sheffield.
- Follow-up or corrections to information should also be reported on a new SAE form and forwarded to the Sheffield CTRU as soon as possible.
- Sheffield CTRU will be responsible for reporting SAEs to the sponsor, the DMEC, and the REC.

If alternative arrangements are required during holiday periods these will be documented in the study specific AE SOP and CTRU will inform site staff.

10.5 CTRU responsibilities

CTRU will be delegated responsibility, by the Sponsor, for the reporting of SAEs to the REC as appropriate. CTRU will also keep investigators informed of any safety issues that arise during the course of the study.

10.6 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter and terms of reference.

11. Statistics

11.1 Sample size, trial adaptations and interim decision rules

Under current practice of conservative management, the mean OHSS-related hospitalisation rate is approximately 41.2% (26/63) based on a retrospective audit of medical records of IVF patients across six IVF fertility units over a year (95% confidence interval, CI: 29.0% to 54.4%). Earlier active management interventions based on uncontrolled small previous studies have resulted in low hospitalisation rates of around 0-8% (12,14,15,28). As such, this trial is targeting a 20% absolute reduction in hospitalisation for early OP to be considered superior to usual care. This targeted 20% absolute reduction is believed to be realistic as previous uncontrolled studies have observed similar or greater effects and, if observed, is more convincing to change clinical practice. Notably, a 20% absolute reduction translates to an odds

ratio (OR) of 0.3825 or relative risk/risk ratio (RR) of 0.512 assuming a 41% usual care event rate. Thus, the targeted effect in terms of OR or RR is a function of the usual care event rate whereas the targeted 20% absolute reduction is consistent across the plausible usual care event rates. An updated preliminary health economics model has indicated that early OP needs to achieve at least between 4.7% to 5.7% reduction in hospitalisation to become cost-saving under several assumptions about the ratio of early to late OHSS and underlying usual care hospitalisation rates assuming a 20% targeted reduction (see Section 11.1.1).

The goal of the trial is to gather convincing evidence about the effects of the early OP that is most likely to change practice regardless of the direction of results. Trial recruitment is expected to be quite challenging so there is a need to pursue the trial only when the study treatment is viewed as promising to use research resources, participants, and time efficiently. This motivated the use of a group sequential design with an option for early stopping for futility (lack of benefit). The decision to stop for futility is non-binding in the sense that it is advisory so it can be ignored or overruled for some reasons without affecting the statistical behaviour of the design (i.e., it does not increase the type I error beyond the budgeted 2.5% for a one-sided test). One interim analysis will be performed when 65% of the maximum sample size has accrued primary outcome data. This delayed interim analysis has been chosen to allow sufficient data to be gathered on hospitalisation rates in both arms to inform reliable interim decisions. The trial will not allow for early stopping for overwhelming benefit (efficacy). Of note, the continuation of the trial after interim analysis does not necessarily imply that early OP is effective, but it only indicates that it is promising and worth pursuing to evaluate further if it is truly effective at the end.

The trial will be stopped for futility if the observed reduction in hospitalisation at an interim analysis is below 4.5% consistent with the updated preliminary health economics model. This stopping rule is constant across plausible usual care event rates and it balances the need to reduce the risk of stopping early for futility when early OP is potentially cost-saving and/or effective with the desire to increase the chances of early stopping when early OP is unlikely to be cost-saving and clinically effective.

Sample sizes were estimated using the rpact R package (29) without continuity correction. The trial will require a maximum total sample size of approximately 224 (112 per arm), rounded upwards to the nearest even number. An interim analysis will be performed when approximately 146 participants (73 per arm) have accrued primary outcome data. This assumes a 90% power, one-sided 2.5% type 1 error rate, 41% usual care hospitalisation rate, 0% dropout rate, a 20% worthwhile and realistic reduction in hospitalisation rate, and a futility threshold of -4.5% (difference in hospitalisation rate). In this case, the trial will be stopped early for futility if the observed reduction in hospitalisation rate at an interim analysis is less than 4.5%. There is only a 1.9% chance of stopping the trial early for futility in error when OP is truly beneficial. Finally, there is a 72.2% probability of stopping early when the effect of OP is the same as usual care (i.e., 41% hospitalisation rate). The operating characteristics of the design under several assumptions that were explored via simulation using a bespoke program in Stata version 16.1 are detailed in an accessible simulation report.

11.1.1 Health Economic Model

The estimated costs of OP and usual care were calculated. For paracentesis these were based on monitoring of symptoms, daily phone calls, a hospital visit for blood

tests, training of participants for monitoring at home, consumables and OP, and a visit to confirm the resolution of symptoms at an estimated cost of £418.74. Usual care included monitoring, blood test, hospital visit for blood tests and a visit to confirm the resolution of symptoms at an estimated cost of £133.10. A hospital visit was estimated to include monitoring, blood samples, hospital admission, rehydration at a cost of £4,092.08 for early onset OHSS based on a length of stay (LOS) of 5 days and the cost of late onset OHSS was £5,870.00 based on LOS of 8 days. Based on data from the audit the mean ratio of early to late hospitalisations was 35 early to 65 late. This ranged for the different sites from 10:90 to 60:40 therefore a variety of ratios were explored these were: 10:90, 25:75, 30:70, 35:65, 40:60, 50:50, and 60:40.

Appendix 1 presents the estimated costs of usual care and OP for alternative ratios of early to late OHSS and for alternative hospitalisation rates. Assuming a reduction of 20% in hospitalisations from OPs the incremental cost difference show that paracentesis is cost saving at a range of £713 to £939. The percentage reduction in hospitalisations required for paracentesis to become cost saving ranged from 5.7% to 4.7% depending on the ratio of early to late OHSS. This informed interim decision rule for futility early stopping described in Section 11.1.

11.2 Statistical Analysis

11.2.1 Analysis of primary outcome: interim and final analyses

The primary analysis will be based on the intention-to-treat principle that will include all eligible participants randomised with informed consent. Although unexpected, any participants with missing primary outcome data will not be assumed to have been hospitalised. The absolute difference in hospitalisation rates between arms is the primary summary measure of the treatment effect of interest although RR and OR (estimated using a simple logistic regression model) will also be presented side by side. At an interim analysis, the unadjusted difference in hospitalisation rates between arms will be calculated to inform the interim decision on whether to stop early for futility. For sensitivity analysis, a mixed effects logistic regression model adjusted for stratification factors (site as a random effect and OHSS severity as a fixed effect) and adjusted difference in hospitalisation rates will be obtained using the delta method via margins (30). For the final analysis of the primary outcome, the unadjusted difference in hospitalisation rates with CI obtained via normal approximation will be reported as well as the p-value from a Chi-squared test. Stagewise ordering will be used for sensitivity analysis to obtain the median unbiased estimate of the difference in hospitalisation rates between arms with the associated 95% CI to be presented alongside the maximum likelihood estimate, if the trial progressed beyond interim analysis. Additional sensitivity analysis will be performed using a mixed-effect logistic regression model adjusted for stratification factors (site as a random effect and OHSS severity as a fixed effect) and adjusted difference in hospitalisation rates post-estimated using delta method via margins. An equivalent binomial regression model with a log link function (i.e., log binomial regression model) and mixed effects generalised linear model of the poisson family with a log link function adjusted for stratification factors (site as a random effect and OHSS severity as a fixed effect) with robust standard errors will be used to estimate unadjusted and adjusted RR with associated 95% CI's respectively. Reporting will adhere to the Adaptive designs CONSORT Extension (ACE) guidance (31,32).

11.2.2 Analysis of secondary outcomes

For progression of OHSS severity, a mixed effects logistic regression model adjusted for stratification factors (site as a random effect and OHSS severity as a fixed effect)

will be used and an adjusted difference in hospitalisation rates will be obtained using the delta method via margins (30). To aid interpretation, measures of treatment effect will be presented as adjusted odds ratio (aOR), adjusted risk difference (aRD) and adjusted relative risk/risk ratio (aRR, using a model described for the primary outcome described in Section 11.2.1) with 95% CIs.
For time to resolution of OHSS assessed within 28 days post-randomisation, Kaplan-Meier curves will be used to visualise the resolution curves between treatment arms and differences qualified using a log-rank test. Median time to resolution by treatment arm with 95% CI will be calculated and reported as summary measures of within group effects. Participants who fail to achieve resolution of symptoms within 28 days post-randomisation will be censored. For sensitivity analysis, a Cox proportional-hazards regression model with shared frailty (site as a random effect) and OHSS severity (as a fixed effect) will be used (if assumptions are met) and treatment effect measure presented as adjusted hazard ratio (aHR) and 95% CIs. Alternative approaches when the proportional hazard assumption is not met will be detailed in the SAP.

For cumulative length of OHSS hospital stay, bootstrapping resampling procedure (accounting for stratification) will be used to obtain the median difference with 95% CI and associated p-value. For patient satisfaction at 28 days, a total satisfaction score will be analysed using a mixed effects linear regression model adjusted for site (as a random effect) and OHSS severity (as a fixed effect), and measure of effect will be presented as adjusted mean difference in satisfaction between treatment arms with 95% CI and associated p-value.

Analysis of safety outcomes (e.g., AEs and SAEs) will be based on descriptive statistics using the safety analysis population defined based on treatment-as-received population.

Detailed analysis of all outcomes including additional sensitivity analysis on the primary outcome will be described in an open-access and pre-specified SAP to be developed and signed off before accessing unblinded data.

11.2.3 Pre-specified subgroups

Subgroup analyse will be performed to explore whether there is heterogeneity in treatment effect on the primary outcome across the following prespecified subgroups:

1) Baseline severity of OHSS (moderate or severe),
2) Whether a participant is taking a preventative drug at randomisation (yes or no),
3) Whether the participant has early or late OHSS at randomisation,
4) Whether the OP procedure was done vaginally or abdominally. For participants who received multiple procedure (which may happen in few cases), this classification will be based on the first performed procedure.

A mixed effects logistic regression model that includes an interaction effect between pre-planned subgroup and treatment group adjusted for site (as a random effect) and severity of OHSS (as a fixed effect) only if it is not a subgroup factor of interest will be used. Details will be included in an open-access and pre-specified SAP.

11.3 Health Economics

11.3.1 Health Economics Analysis

Analyses will be conducted in conjunction with the health economic analysis plan (HEAP). Two HEAPs will be produced, one in relation to the interim analysis, and one relating to the end-of-trial analysis.

The primary cost-effectiveness analysis will present cost per hospitalisation avoided, comparing early active outpatient management for women with early or late moderate or severe OHSS. The feasibility of conducting a cost-utility analysis will be explored in the feasibility study, and if feasible, the results will also be expressed as incremental cost per quality-adjusted life years (QALY) gained. An interim health economic analysis will be performed when 65% of the maximum sample size has accrued. The aims of the interim analysis will be to update the pre-trial model and to examine the cost-effectiveness of OP compared to usual care. The QALY will be calculated using the EQ-5D-5L questionnaire administered daily until resolution of symptoms and then at 28 days post randomisation. Based on NICE's recent position statement, van Hout et al.'s scoring algorithm will be used to obtain utility scores from responses to the EQ-5D-5L (33).

Women will be asked to complete resource use questionnaires at 28 days post randomisation asking for data from the preceding month. Women will also be asked to complete a patient cost at 28-day follow-up about their last visit to their fertility doctor. Further resource use data will be collected during the trial to inform the health economics analysis, on areas including training of staff and participants on the trial and consumables given; details of monitoring given to participants; outpatient treatment delivery details; hospital admission information and treatment received. Unit costs will be derived from appropriate national sources including NHS reference costs and Personal Social Service Research Unit costs (34,35). The resource use questionnaire will be designed for this study and draw on data collection tools developed in ScHARR.

Analyses will be undertaken from the NHS and personal social service (PSS) perspective as recommended by NICE (36) and will follow recommended methods and good practice guides (37,38). The primary analysis for both Sub-Protocols within the trial will be a within-trial analysis using data from the trial. A secondary analysis will consider a decision tree based analysis, similar to those used by Casals et al., and Csokmay et al. (4,39), that extends costs and outcomes over a 12 month time horizon. Incremental differences between costs and effectiveness/QALYs between those receiving OP and those receiving usual care will be described and the incremental cost effectiveness ratio (ICER) will be calculated. Results will allow for uncertainty using bootstrapping and probabilistic sensitivity analysis. Sensitivity analyses and subgroup analysis will be undertaken by varying values on uncertain and assess their impact on the ICER estimates.

12. Ancillary sub-studies

12.1 Qualitative study to improve recruitment

12.1.1 Aim:

To facilitate the feasibility of conducting the RCT by identifying potential problems with recruitment to the RCT, so that solutions can be instigated rapidly.

12.1.2 Objectives

1) Identify optimal and sub-optimal practice for recruitment to this trial using audio recording of recruitment sessions

2) Gather information about numbers approached and numbers who consent to participate in the trial by assessment of anonymised recruitment logs and other trial documentation
3) Identify any problems with the recruitment process by interviewing recruiting healthcare professionals
4) Explore the experiences of women being recruited into the trial by interviewing both women who consented, and women who declined, to participate in the trials.

12.1.3 Background:

Research has shown that information conveyed during RCT recruitment sessions varies considerably in content and quality (40). Qualitative research has been used to explore variation, identify problems, and recommend solutions (41). We will undertake qualitative research concurrently with the internal pilot in order to maximise recruitment to the trial. We will use the Quintet Recruitment Intervention (QRI) (42,43). This optimises recruitment and informed consent where recruitment difficulties are anticipated. Problems can be identified rapidly and tailored solutions designed while an RCT is in progress. It is undertaken in two stages.
As part of this study, in addition to interviewing women who agree to participate in the STOP-OHSS trial, we will also be interviewing women who declined to take part in the trial, in order to identify some the varied reasons for not participating. Other researchers have interviewed people who have declined to participate in RCTs. For example, qualitative research alongside an RCT of psychological theory for depression showed that people declined because they did not think they were eligible, or they felt they did not have potential to benefit (44).

12.1.4 Methods

Data Collection

Audio recording of 10-12 trial recruitment sessions:
Encrypted audio-recorders will be used and prior to the process patients will be given an information sheet with details of how the recording data will be used, and how the data will be stored. Patients will be asked if they consent to the sessions being recorded and asked to sign a consent form to confirm this.

Interviews:
Qualitative semi-structured interviews will be conducted either by telephone, or another remote virtual method, dependant on participant preference. The option for a face-to-face interview can also be provided if participants have a strong preference for this and are unlikely to participate otherwise.

Interviews will be audio-recorded on an encrypted digital recorder. Reflexive notes will be made during and after the interviews. It is anticipated that the interviews (HCP and patient) will last approximately 30 minutes. The interviews will be transcribed and anonymised.

Topic guides for all interviews will focus on how people found the recruitment process, any problems they identified with it, and potential solutions to address these problems.

Sample

4-6 centres will be chosen based on diversity including NHS and private fertility treatment clinics, small and large centres, high and low recruitment rates.

Healthcare Professionals (HCP) with recruiting responsibilities interviews:
n=6-8 interviews with a variety of healthcare professionals who have responsibility for recruiting women to the STOP-OHSS trial (doctors, clinical nurse, Research Nurses/Midwives). We would aim for 1-2 HCP from each centre in the sample.

Inclusion criteria for HCP
Experience of approaching women to participate in the STOP-OHSS trial – must have approached a minimum of 3 potential participants

Women with OHSS interviews:
8-10 Women who have had OHSS and experienced the trial recruitment process, 4-5 who have agreed to participate in the trial, and 4-5 who declined to take part.

Inclusion criteria for women with OHSS
Women diagnosed with moderate to severe OHSS who have been approached to take part in the STOP-OHSS trial
Women who's OHSS symptoms have settled from an acute phase (after symptom resolution visit)
Aged 18 and over
Able to read and understand a good level of English so that they are able to give informed consent and participate in an interview conducted in English

Recruitment

Health Care Professionals (HCP):
HCP with recruiting responsibilities at participating centres will be identified by the trial team, and approached with information about the study. They will be given a letter introducing the study and participant information sheet, with the research team contact details. They will be asked to contact the research team if they would like to take part in an interview.

Women who have agreed to participate in the trial:
As part of the consent to participate in the STOP-OHSS trial women with OHSS will be asked to indicate on the consent form if they agree to be contacted by the trial team regarding participation in an interview. The trial team will contact only those women who have consented to contact with information about the interview study. Women will only be contacted about taking part in an interview after they have had their symptom resolution visit, to avoid additional burden whilst they are experiencing symptoms. They will be given a participant information sheet (with researcher contact details), and asked to contact the research team if they would like to take part in an interview.

Women who declined to take part in the trial:
At the point that a woman declines to take part in the trial the recruiting HCP will give a brief explanation about the interview study and they will be given an information pack containing a letter introducing the study, a participant information sheet (with researcher team contact details). They will be asked to contact the research team if they would like to participate in an interview. We will take care when approaching

women who have declined to participate in the RCT to ensure they understand that we are not trying to change their minds and respect their decision.

Consent:
Written informed consent will be obtained from all participants in the form of an electronic consent form sent prior to the interview. If participants do not have an email address to be able to access the consent form then audio consent will be taken at the start of the interview, and recorded, and the researcher will complete the consent form on their behalf.

Data Analysis
We will record and transcribe interviews and recruitment sessions, and identify any problems with recruitment, and develop potential solutions. For example, from the recorded recruitment sessions this may involve analysing the language used to describe the trial and interventions, exploring what questions potential participants have about the information they are given, and listening to the explanations and response given to any questions.

We will also examine anonymous recruitment logs and patient facing information given to participants in case they can confirm or further elucidate any problems identified in the recruitment session or interviews.

Based on the information gathered from the interviews, and recorded recruitment sessions, we will design an action plan with the relevant team members to address problems identified. This action plan may involve further training for recruiters or amendments to the PIS for use across all centres.

Data collection and analysis will be ‘dynamic’ and iterative in that learning from the qualitative research will be fed back to the team for discussion to identify solutions for the RCT conduct, solutions will be instigated, and recruitment logs used to assess the impact of these changes. Analysis will need to be rapid. Close team working with key members of the team, including PPI (Public and Patient Involvement) members, will be essential during this process.

Recruitment Process for Women who agreed to Trial Participation

1. •Women will indicate consent to be contacted about taking part in an interview as part of the overall trial consent process.
2. •Women that have consented will be contacted by the trial team after their symptom resolution visit in the trial, with an email/letter/phonecall introducing the study and sent a PIS with the research team contact details.
3. •Women will contact the research team directly if they would like to take part in an interview.

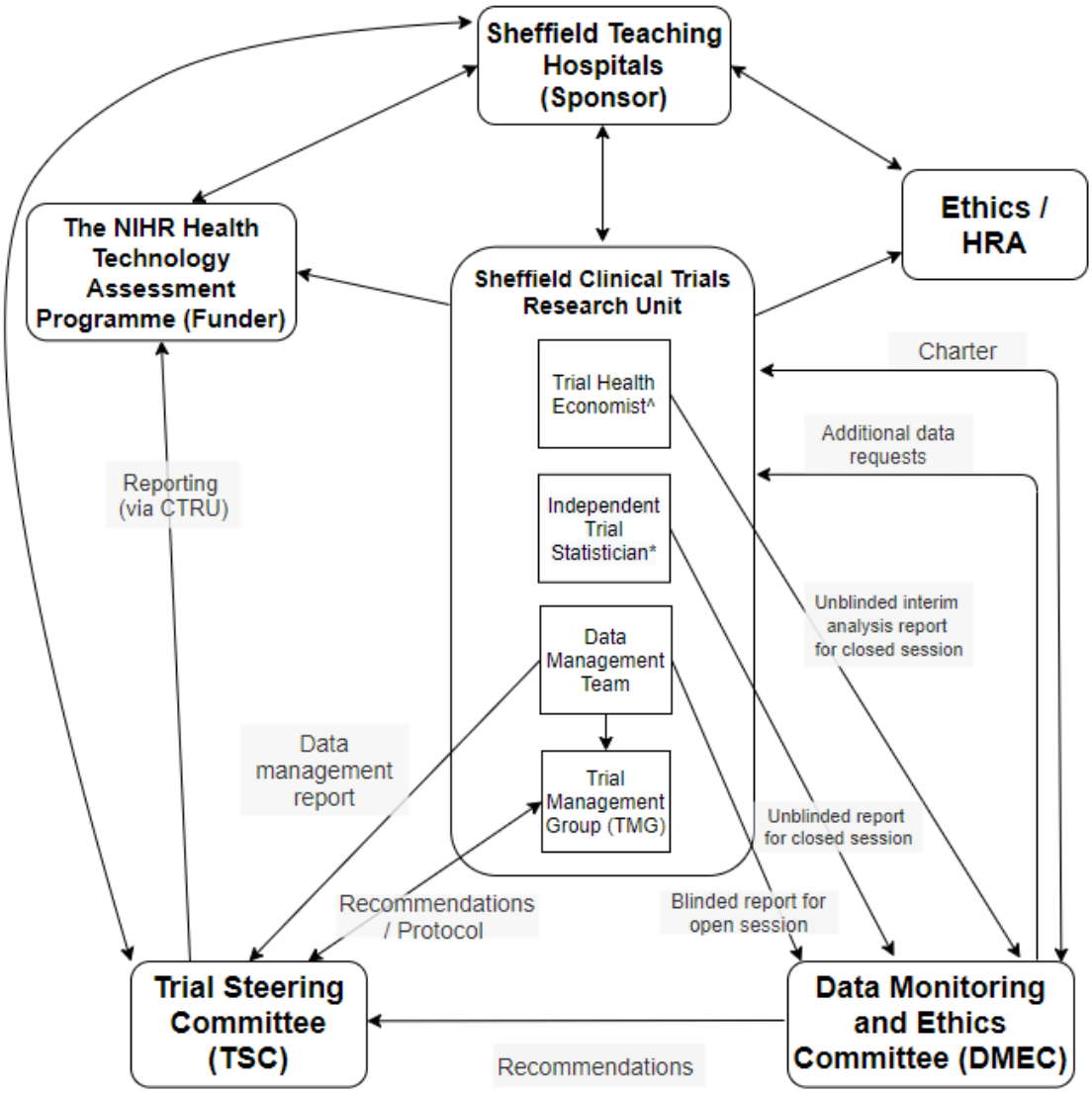
Recruitment Process for Women who Declined Trial Participation

1. • At the point that a women declines to take part in the trial the recruiting HCP will give a brief explanation about the interview study.
   • They will also be given an information pack containing a letter introducing the study, and a PIS (with research team contact details).
2. • Women will contact the research team directly if they would like to take part in an interview.
3. • Care will be taken when approaching women who have declined to participate in the RCT to ensure they understand that we are not trying to change their minds and respect their decision.

13. Trial oversight

The oversight bodies on the STOP-OHSS trial work according to the following diagram:

Figure 1 Structure of STOP-OHSS Trial Oversight



^The Trial Health Economist will be blinded until the interim analysis timepoint when they will conduct the interim analysis on unlbinded data and report to the DMEC.
*A statistician independent of the conduct of the STOP-OHSS trial. They will be responsible for conducting interim analysis and preparing unblinded monitoring reports for the DMEC.

13.1 Trial Steering Committee

The role of the TSC is to provide supervision of the protocol, SAP and HEAP, to provide advice on and monitor the study, to review information from other sources and consider recommendations from the DMEC and make recommendations on closing the trial

prematurely. The TSC will meet at regular intervals, as defined in the TSC terms of reference. The CI, Statistician, CTRU Oversight, Trial Manager, Sponsor Representative will be invited to the TSC, in addition to an independent Chair, clinical, health economics expertise, statistical expertise and PPI representation.

13.2 Data Monitoring and Ethics Committee

The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required and will be given an opportunity to review the SAP and HEAP. Details of their roles are responsibilities are described in the DMEC charter.

Details of the interim analysis including adaptive features, adaptation rules, and when interim analysis will be performed are described in Section 11.1. The DMEC may recommend to the TSC or funder during the interim analysis or another point that the trial is stopped or modified on the basis of data or on safety grounds. The DMEC will meet at regular intervals, as defined in the DMEC charter. The DMEC will be run in-line with Sheffield CTRU SOP GOV003 Data Monitoring and Ethics Committee and SOP DM009 Data Management Plan. The DMEC will have access to all data, including blinded data.

13.3 Trial Management Group (TMG)

The trial will be supervised on a day-to-day basis by the TMG run in accordance with SOP GOV001 Trial Management Group. This group reports to the TSC. At each participating centre a local PI will report to the TMG via the staff at the Sheffield CTRU. The core TMG will meet regularly approximately once every two months but rising to at least once per month before key milestones (ethical approval, recruitment initiation etc).

The CI, Lead Research Nurse, CTRU Oversight, Study Manager, Statistician, Health Economist, Qualitative Researchers, Research Nurses, Data Management and co-applicants will be invited to the meetings.

In addition, investigator meetings will be set up during the recruitment phase of the study, at least once every two months, where the site PIs (or another delegated individual) will discuss pertinent issues with the research team, including recruitment, data completion and intervention delivery.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the UK Data Protection Act (DPA) 2018 will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield CTRU who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (SOP DM009 Data Management Plan).

Study participants will be assigned a unique study ID number at screening to identify them throughout the study, and to link all of their clinical information recorded on the study database and on any paper CRFs, as well as any correspondence between CTRU and participating centres about them.
Data will be entered onto the study database. The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. The trial manual provided to all sites to support trial procedures and documentation will provide further information on the requirements of source data.

Central study staff may send participants questionnaires either as links to online surveys or as posted booklets. Returned paper booklets will be stored centrally in restricted-access filing cabinets and entered by central study staff on to the study database. Study records will be stored for 15 years after the completion of the study before being destroyed.

14.1 Archiving

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (SOP PM012 Archiving). Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

15. Data access and quality assurance

The study database will reside on Prospect, Sheffield CTRU's in-house data management system. Prospect uses industry standard techniques to provide security, including password hashing and encryption of data transmission using SSL/TLS. Access to the system is controlled by usernames and passwords, and comprehensive privilege management ensures that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data.

A member of staff at each site will enter data from source documents into the study specific Prospect database when available. Validation rules will be defined within Prospect, and automated validation reports will regularly check the data against these rules: discrepancies will be generated for site and central staff to look into. Discrepancies will be tracked and resolved within the system. All data entries and corrections are logged within the electronic audit trail.

Participant names and contact details will be collected and entered on the database in order to facilitate follow-up data collection. Access to these personal details will be restricted to users with appropriate privileges and will not be included in the data exported from the database for analysis.

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained.

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital or Fertility Centre at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatment, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF). Staff should also have completed GCP training within the last three years, ensure this is renewed every three years, and copies of the GCP certificate are held within the ISF and TMF.

Before each site is activated, capability to conduct the trial will be assessed and documented using a site assessment form. The CTRU will arrange a site initiation with each site, which may be carried out face-to-face or remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk Assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures.

15.3 Reporting serious breaches and non-compliances

A "serious breach" is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC and, writing within 7 days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware in-line with (SOP PM011 Protocol and GCP Non-Compliances & Serious Breaches).

15.4 Site monitoring

On-site and/or remote monitoring will be performed according to the STOP-OHSS Site Monitoring Plan and in-line with the Sheffield CTRU Site Monitoring SOP (SOP QA001 Site Monitoring).

Regular monitoring of sites will occur throughout the study as specified in the STOP-OHSS Site Monitoring Plan and additional monitoring will be undertaken where required. Site monitoring will include reviewing activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the participant are being protected and

3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against medical records/site file etc. by the Study Monitor (source document verification). The Study Monitor will inspect eCRFs (either on-site or remotely) throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the eCRFs. A remote review of a sample of consent forms will also be completed, and sites will be requested to send consent forms to CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial.

A close-out visit (on-site or remote) will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

CTRU staff will also complete central monitoring which will include a review of entered data for possible errors and missing data points.

15.5 Data Sharing Statement

Data access requests will be reviewed and authorised by a sub-committee of the Trial Management Group (TMG) while the trial is on-going and by the Sheffield CTRU in conjunction with project collaborators after the trial has ended.

16. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

Full details of publications and dissemination to participants, healthcare professionals and the public, including guidance on authorship, are documented in a Publication and Dissemination Plan.

17. Finance

STOP-OHSS is funded by the UK NIHR Health Technology Assessment (HTA) Programme (project number NIHR128137) and details have been drawn up in a separate agreement. The views expressed are those of the author(s) and not necessarily those of NIHR or the Department of Health and Social Care. Participants can be reimbursed for the cost of reasonable travel expenses. Further details are included in the site agreement.

18. Ethics approval

Before initiation of the study at participating sites, the protocol, informed consent forms and information materials to be given to the participants will be submitted to an NHS REC and to the Health Research Authority (HRA). Any further amendments will be submitted and approved by the HRA and REC as relevant.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place locally (SOP RA003 Ethical and Regulatory Approvals).

Important protocol modifications (e.g. changes to eligibility criteria, outcomes and analyses) will be communicated to relevant parties including funders, investigators, REC, HRA, and trial registries.

19. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

The green light to begin recruitment of study participants at a site will not be issued until a letter of local R&D Confirmation of Capacity and capability (CCC) has been issued, a Site Initiation Visit (SIV) has taken place and access given to site staff for the database. Green light provision has been delegated to CTRU by the sponsor.

20. Trial Organisation and Responsibilities

20.1 Principal Investigators

Each site will have a local PI who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

COVID-19

Site PIs will be responsible for ensuring that local policies and procedures are followed in relation to the COVID-19 pandemic.

20.2 Nursing co-ordinator each site

Each participating centre should delegate a Research Nurse/Midwife/Associate PI/Dr as the local Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, and that patients are provided with study information sheets and given the opportunity to discuss the study if required. The Research Nurse/Midwife may be responsible for the collection of data and follow-up evaluations.

20.4 Central nursing research team

The central research nursing team may support sites locally by discussing the trial with potential participants, taking consent, performing randomisation and collecting follow-up data. A 'consent to contact' process will be used to facilitate this; women may be told about the study initially by a member of the local research team and be given the option to receive further information from a member of the central research nursing team. If this option is pursued, the woman will be asked to give consent for their contact details to be given to a member of the central research nursing team (consent to contact) only once the PI has confirmed trial eligibility.

20.4 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation system design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU Trial Manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability approval has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

21. Patient & Public Involvement

During the outline and full stages of the grant application for this trial, women who experienced OHSS during their fertility journey were asked for their input/comments. The study was reviewed by The Reproductive Health Research Public Advisory Panel (PPI) at the Jessop Wing – Sheffield, who will continue to provide support throughout the trial, and the PPI co-applicants. We have PPI representation on the TMG, which meets approximately once every two months plus PPI representation on the TSC, which will meet approximately every six months. Guidance and advice will be sought throughout the course of the trial including requesting PPI input into the development of participant facing materials and dissemination of trial results.

22. Indemnity / Compensation / Insurance

Both the Sponsor (Sheffield Teaching Hospitals) and the University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment which is provided.

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Appendices

Appendix 1: Cost estimates for usual care and outpatient paracentesis

	Hospitalisation ratio early: late OHSS						
	10 : 90	25 : 75	30 : 70	35 : 65	40 : 60	50 : 50	60 : 40
Hospitalisation cost	6122.165	5783.818	5671.035	5558.253	5445.47	5219.905	4994.34
Usual care + 30% Hospital	1969.75	1868.245	1834.411	1800.576	1766.741	1699.072	1631.402
Usual care + 35% Hospital	2275.858	2157.436	2117.962	2078.488	2039.015	1960.067	1881.119
Usual care + 40% Hospital	2581.966	2446.627	2401.514	2356.401	2311.288	2221.062	2130.836
Usual care + 45% Hospital	2888.074	2735.818	2685.066	2634.314	2583.562	2482.057	2380.553
Usual care + 50% Hospital	3194.183	3025.009	2968.618	2912.226	2855.835	2743.053	2630.27
Assuming 20% reduction in hospitalisation							
OP + 10% Hospital	1030.957	997.1218	985.8435	974.5653	963.287	940.7305	918.174
OP + 15% Hospital	1337.065	1286.313	1269.395	1252.478	1235.561	1201.726	1167.891
OP + 20% Hospital	1643.173	1575.504	1552.947	1530.391	1507.834	1462.721	1417.608
OP + 25% Hospital	1949.281	1864.694	1836.499	1808.303	1780.108	1723.716	1667.325
OP + 30% Hospital	2255.39	2153.885	2120.051	2086.216	2052.381	1984.712	1917.042
Incremental costs OP – Usual care*	-938.793	-871.124	-848.567	-826.011	-803.454	-758.341	-713.228
	-938.793	-871.124	-848.567	-826.011	-803.454	-758.341	-713.228
Note incremental savings are the same	-938.793	-871.124	-848.567	-826.011	-803.454	-758.341	-713.228
regardless of % hospitalisation owing to	-938.793	-871.124	-848.567	-826.011	-803.454	-758.341	-713.228
difference being 20% for each calculation	-938.793	-871.124	-848.567	-826.011	-803.454	-758.341	-713.228
Reduction in hospitalisation at which OP becomes cost saving	0.046657	0.049386	0.050368	0.05139	0.052455	0.054721	0.057193
% reduction	4.66567	4.938607	5.036823	5.139025	5.245461	5.47213	5.719274

* Note incremental savings are the same regardless of % hospitalisation owing to difference being 20% for each calculation