# A retrospective review of patient notes to establish the usual care of Ovarian Hyper-Stimulation Syndrome and the feasibility of the full STOP-OHSS Randomised Controlled Trials: Protocol v2, 19/09/20

## 1. Background

### What is Ovarian Hyper-Stimulation Syndrome (OHSS)

Ovarian hyperstimulation syndrome (OHSS) poses one of the greatest risks to women undergoing assisted reproductive treatments (ARTs, including In Vitro Fertilisation (IVF) and Intra Uterine Insemination (IUI)). OHSS usually occurs in women who have over responded to ovarian stimulation drugs. It is triggered by the effect of Human Chorionic Gonadotropin (hCG) either administered during treatment to trigger the maturation of the oocytes (the eggs) or produced naturally as a result of 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. 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 death [1].

OHSS can be further clinically classed into early and late. STOP-OHSS trial definitions are based on the Royal College of Obstetricians and Gynaecologists Greentop Guidance on the management of OHSS [2]. Early OHSS is caused by the ovarian stimulation drugs given during ARTs and occurs usually up to 8 days of the final trigger drug (hCG) being given and before embryo transfer has taken place. Late OHSS usually occurs more than 9 or more days after the trigger drug is given and/or if it occurs after embryo transplantation and they are potentially pregnant.

OHSS can be classified into different levels of severity. STOP-OHSS trial definitions (again based on the Royal College of Gynaecologists Guidance) are currently that mild OHSS involves abdominal bloating, mild abdominal pain and an ovarian size of below 8cm. Mild forms of OHSS are fairly common affecting approximately 1:3 women undergoing IVF treatment. Moderate and severe OHSS, although less common (up to 8% for moderate and severe OHSS combined)[2], can have a significant impact on a woman's health resulting in prolonged hospitalisation and posing a significant economic burden on both patient and NHS resources. Moderate OHSS do not meet the criteria of severe and can be defined as having: moderate abdominal pain; fluid accumulation in the abdomen (ascites), confirmed by ultrasound scan and increased ovarian size (8-12cm). Moderate patients may also have nausea with or without vomiting. Patients with severe OHSS would have clinically detectable fluid (clinical ascites) and one of the other features: low urine output, ovarian size of above 12cm, or a haematocrit level above 0.45. Critical OHSS can be distinguished by patients having clinical ascites with one of the following features: large hydrothorax, haematocrit level above 0.55, white cell count of over 25000/ml, very little or no urine, thromboembolism or acute respiratory distress syndrome.

### The STOP-OHSS Clinical Trials

The STOP-OHSS clinical trials plan to test whether earlier active outpatient management interventions for women with moderate to severe, early or late OHSS are acceptable and feasible, and what is the clinical and cost-effectiveness of such interventions compared to conventional conservative

management. Specifically, in the later OHSS patients, early signals of clinical efficacy and cost-effectiveness will be explored. Evidence [3–10] indicates that earlier active outpatient management may help treat OHSS when compared to current management which is conservative and typically involves monitoring the patient until the condition becomes severe and admitting them [2]. We will run two trials – the first is definitive within the early OHSS population ("Early OHSS Trial"), the second is exploratory within the late OHSS population ("Late OHSS Trial"). The inclusion and exclusion criteria for the future trials are in development.

### The need for a review of patient notes

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 [2]. However, accurate numbers of women suffering from OHSS are not available. In a 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 period [11]. OHSS may be under-reported as a result of women being admitted to units other than those where they had their fertility treatment. This could result in the loss of follow up data. There is also a paucity of data relating to hospitalisation rates within 28 days which is the primary outcome for the future trials. Due to the lack of accurate data on incidence and hospitalisation, the initial estimates made to calculate the sample sizes needed for the planned RCTs and to understand the statistical behaviour of the designs, and to decide how many sites would be needed to recruit these numbers, and whether the trials are feasible may be unreliable.

Data gathered from sites during the application phase on incidence of moderate and severe OHSS and hospitalisation need to be confirmed with a more thorough investigation of patient notes. We need to confirm that the trials are feasible and sample size assumptions used are reliable, designs are appropriate to address research questions under those reliable assumptions, and patient throughput will be sufficient to recruit the required sample sizes. If, after the review of patient notes, the estimate of the incidence of moderate and severe OHSS or hospitalisation rate within 28 days are significantly changed, an amendment may be needed to the number of centres or recruitment period (either increased or decreased) and study design – or alternatively, the trials may be deemed infeasible.

Gathering information about usual care protocols and practice will contribute towards a consensus-building process within Phase 1 of the trial to agree upon the treatment protocols to be used in the trial. The data will also be used to understand whether sites are already giving the proposed interventions as part of their usual care, in order to inform discussions around site set-up. We also collect usual care data to understand variation in usual care across sites which is key in interpreting future results from both trials.

## 2. Aim and objectives

### Aim

To conduct a robust review of patient records at our collaborating centres to inform the design of the STOP-OHSS clinical trials and to assess feasibility of conducting these trials.

### Objectives

To contribute to Phase 1 of the STOP-OHSS study by:

1. Describing usual care across participating fertility units and assessing variability
2. Validating planned study design parameters for both RCTs, specifically by:
    a. determining the incidence of moderate/severe and early/late OHSS cases who would be eligible for the RCTs

b. determining hospitalisation rates of those patients identified in (a).

## 3. Methods

Data will be collected in two ways:

a) By requesting usual care protocols (SOPs) via email, and
b) By requesting completion of an excel database with information about potential cases of moderate and severe OHSS that occurred over a one-year period between 1 March 2019 and 29 Feb 2020, a period prior to the Covid-19 outbreak in the UK.

In order to complete (b) above, sites will be asked to conduct searches in their local databases (such as IDEAS Fertility Clinic Software) that will help them to identify patients that may have experienced moderate or severe OHSS (see data entry guide for search information). Sites will be asked not to search based on hospital admission, as this may lead to overestimation of the true hospitalisation rate. Centres will be asked to record the searches they used to locate the patients and to enter *all* patients returned as a result of these searches in the database.

The database will collect information about the patient's IVF cycle, symptoms of OHSS, diagnosis, blood test results, out-patient treatment and hospital admission. It is designed to understand the patient's trajectory and development of symptoms, and to collect information relating to the trial's inclusion and exclusion criteria. Further design aspects include that most options are drop-down multi-choice options to standardise answers and there are comments boxes to provide further information. Sites are asked to label anyone who has undergone more than one cycle in that year with a specific labelling format to make this clear.

Sites are given a guidance document and training films and asked to complete and return the database to the Trial Manager at Sheffield CTRU.

A Master database will summarise returned data across all sites.

## 4. Sample

In this case, as the exercise is meant to understand the feasibility of the STOP-OHSS trial, we will ask all centres interested in taking part in the clinical trial to complete this. We estimate that a maximum of 20 centres may complete the review, but would consider other centres completing it if they are interested in the trial or are on our reserve list.

## 5. Analysis

On receiving back the data from the sites, we will first conduct quality control to view the data and the search history and go back to sites with any questions about missing data or unclear answers.

We will use the data provided by the sites to calculate incidences of moderate and severe OHSS per year, the number of potentially eligible patients in the early and late OHSS population per year, and the proportion of eligible patients that were hospitalised within 28 days with uncertainty (e.g. 95% confidence interval estimated via Wilson score method[12] ref). Descriptive statistical analysis will be used to analyse the data.

SOPs will be analysed using NVIVO or a similar programme and data presented both statistically and textually. Usual care pathways used will be categorised and summarised, presenting information including the number and proportion of sites giving early outpatient management as part of usual care, and contextual information of interest to the trial, including definitions of OHSS types, resolution of symptoms, criteria for hospitalisation.

A detailed quality assurance and data analysis plan has been produced separately to further outline processes.

## 6. Anticipated Impact and Dissemination

The findings from this review of patient notes will be fed back to clinicians as part of a consensus-funding process and meeting in order to confirm treatment protocols that will be acceptable to sites. Master spreadsheets and data arising from this study will be presented to the TSC, DMEC and funders as part of a STOP/GO assessment to assess whether the trial should continue in 2021. Usual care pathway data will also be used within the main clinical trial to describe current usual care and enable use to interpret the trial results correctly.

The review will provide reliable data on moderate and severe OHSS including early and late population which could be used for future treatment, research and decision-making. As such, we aim to publish a journal article. The work may also be presented at conferences and within other journal articles.

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# STOP-OHSS – A qualitative study to understand the acceptability and feasibility of new earlier active management treatment of Ovarian Hyper-Stimulation Syndrome (OHSS) v1.1 15/06/20

## Aim

To explore the acceptability and feasibility of earlier active outpatient management interventions for women with moderate to severe, early or late ovarian hyper-stimulation syndrome (OHSS)

## Background

What is Ovarian Hyper-Stimulation Syndrome (OHSS)

Ovarian hyper-stimulation syndrome (OHSS) poses one of the greatest risks to women undergoing assisted reproductive treatments (ARTs, including In Vitro Fertilisation (IVF) and Intra Uterine 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, develop cysts (fluid filled sacs) and fluid leaks into various body cavities.

OHSS can be clinically classified as early and late. Early OHSS is usually caused by the ovarian stimulation drugs given during treatment, and usually occurs within 7 days of the final drug given (called hCG). 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 [1]. Although mild forms of OHSS are fairly common (approximately 1:3 women undergoing IVF treatment), more severe OHSS, although less common (up to 8% for combined moderate and severe OHSS) [2] can have a significant impact on a woman's health resulting in prolonged hospitalisation and posing a significant economic burden on both patient and 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 [2]. Although the mean hospital stay is approximately 3 days [1], the duration of stay can be much longer [3].

Current treatments

Currently, treatment is only usually provided once the condition has progressed to a severe state and the patient may require intensive inpatient treatment. OHSS can be classed as 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 death [4].

Admission often results in a significant number of laboratory investigations and blood tests 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 of time cannot be overstated and neither can the burden of investigations and interventions necessary on the NHS.

Currently, clinical practice usually involves monitoring the patient until the condition becomes severe, at which point the patient is most likely to be admitted to hospital, as recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) green top guideline [2]. 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 not only improves symptoms but the overall condition.

The potential of early management

Previous uncontrolled small studies [8–13] have shown that outpatient paracentesis can prevent the need for hospitalisation if undertaken prior to the condition requiring intensive in-patient treatment. Similar evidence exists from oncology studies to support this outpatient management strategy that has shown the safety and feasibility of outpatient drainage of ascites in women with malignant ascites [14]. Gonadotropin releasing hormone (GnRH) antagonists have also shown promising results for the earlier treatment of moderate and severe OHSS - several uncontrolled small studies have examined the luteal phase administration of GnRH [15–18] which is thought to act through a significant decline in vascular endothelial growth factor (VEGF), causing resolution of the pathophysiological changes of OHSS [19]. If intervention at the moderate stage is shown to be acceptable, safe, effective and cost effective, then it may have benefits to women, their families and the NHS.

At the moment, the majority of clinicians would intervene for severe OHSS by hospital admission and inpatient management [2]. To be able to manage these patients in an outpatient setting requires a level of confidence and change in attitudes that can only be changed by providing high quality evidence within a large randomised control study 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 for severe OHSS 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. The early treatment of moderate OHSS where no treatment usually occurs will require active engagement in treatment by women themselves.

## A qualitative study as part of a wider evaluation of OHSS

This qualitative study forms part of a feasibility study (phase 1) to develop clinical protocols for the delivery of paracentesis and GnRH antagonists in an outpatient setting. The findings will feed into two RCTs that will trial new early, active treatment pathways for women with OHSS. We have involved patient groups, and particularly women who have personally experienced OHSS in the development of this wider study.

**Aim:** To explore the acceptability and feasibility, to patients and healthcare professionals (HCP), of early active intervention for moderate or severe OHSS occurring at an early or late stage.

**Objectives:**

1. To explore the personal experiences of women who have had OHSS
2. To explore the acceptability to women of the proposed treatment protocols
3. To explore the views of women about the proposed RCTs
4. To identify current experiences of HCPs managing and treating OHSS
5. To ascertain HCPs views of the proposed treatment protocols
6. To explore HCPs views about the proposed RCTs and their local feasibility

### Methods:

Qualitative interviews with HCPs (Doctors, Clinical Nurses and Research Nurses/Midwives) and women who have had OHSS. Data collection and analysis will be 'dynamic' and iterative in that learning from the qualitative research will be fed back to the research team developing the treatment protocols for discussion to identify potential changes to the interventions or RCT designs; then changes will be made to descriptions offered within later interviews.

**Sample:**HCP interviews (n=12-15) – Doctors, Clinical Nurses and Research Nurses/Midwives from 6-8 centres will be interviewed. The centres will be chosen based on diversity including fertility treatment offered in NHS and private clinics, centres with experience of early management or not, small and large centres, and high and low incidence of OHSS.

Women with OHSS interviews (n=12-16) – Women who have had early or late, moderate or severe OHSS that did, and did not, result in hospitalisation. Women will be purposively selected for early and late stage OHSS (n=6-8 early, n=6-8 late).

| Inclusion criteria for patients | Exclusion criteria for patients |
|---|---|
| Women diagnosed with moderate or severe OHSS – early or late category | Critical OHSS |
| Aged 18 or over | Under 18 |
| Able to read and understand a good level of English so that they can give informed consent and participate in an interview conducted in English | Unable to read or understand English |
| Approximately 1 month post OHSS – when most acute symptoms are more likely to have settled | Whilst still acutely symptomatic of OHSS |
| Diagnosed with OHSS in the last 18 months | Diagnosed with OHSS over 18 months ago |

**Recruitment:**

HCP recruitment

The lead contact in each site will be asked by the central research team to undergo an interview and to identify other HCPs involved in managing OHSS and/or fertility related RCTs within the site to be invited for interview. These contact details will be sent to the qualitative research team who will then contact those people directly with an introductory letter with information about the study, a participant information sheet, researcher contact details and also to find out if they have any questions, if they want to participate and to arrange an interview. HCPs will be able to contact the researchers either electronically or via telephone to ask any questions and indicate if they would like to take part, and to arrange an interview.

Patient recruitment

Women who have recovered from OHSS will need to be treated with sensitivity throughout the process from recruitment through to data collection. Fertility treatment, OHSS and hospitalisation are stressful and emotional experiences for women and their families. We have worked closely with PPI members to help to identify procedures for approaching women for participation in these interviews and for their input on how best to conduct interviews with sensitivity.

A HCP at each fertility treatment centre will identify women with OHSS from clinical records, or during outpatient and other clinic visits.

*Recruitment from clinic*

If identified in clinic the site HCP will give the potential participant a brief introduction to the study and ask if they would like further information. If they would the HCP will give or email them an introductory letter, a participant information sheet which has the research teams contact details on it, and a response card and FREEPOST return envelope if given in person.

*Recruitment from medical records*

If identified through medical records, the HCP will contact the potential participant either via telephone or through the post. If first contact is made over the phone the HCP will give a brief introduction to the study and ask if they are interested in receiving further information. If the patient is interested the HCP will send to the patient (via post or email) an introductory letter, participant information sheet which has the research team contact details and a response card (with FREEPOST return envelope if by post).

If the HCP makes first contact through the post or email they will send a letter of introduction about the study, the participant information sheet with research team contact details and the response card (with FREEPOST envelope if by post).

The recruitment process can be seen in Appendix A.

Patients will be able to indicate their interest in participating by returning a response card to the research team either by email or in a FREEPOST envelope that will be included with their information pack, or by contacting the research team directly.

Interviews with patients are likely to take place at least one month after OHSS occurred to ensure the women have had time to recover from the acute aspects of the OHSS episode and/or hospitalisation. Patients will also be recruited from historical cases of OHSS in the last 18 months.

*Recruitment from advertisement*

We may ask relevant organisations (for example, those related to fertility such as fertility network UK) to display an advertisement for us in their newsletters, websites, social media (including Facebook). Contact details for the central study research team will be included in the advert and potential participants will contact the team directly if they are interested in participating, or require further information. When potential participants contact the research team they will be told more about the study, and their contact information taken so that the research team can send them the PIS and consent form. They will also have the opportunity to ask any questions. At this point the research team will ask potential participants screening questions about when they experienced OHSS, the type of clinic they attended, and if the OHSS was early or late, to check their eligibility and enable sampling, and arrange a suitable time for interview.

**Consent and Data Collection:**

For both patients and HCP qualitative semi-structured interviews will be conducted face-to-face, via telephone or an online communication platform such as Skype.

Prior to the interview, the researcher will confirm that the participant has understood the information sheet and ask if they have any further questions. For staff, they will return the e-consent form by email. Researchers will sign the document and return a copy to staff for their records. Patients will have the option of returning the signed consent form either by post, email or in person at the interview. During the COVID-19 pandemic patients will give verbal consent at the beginning of the interview which will be recorded. For verbal consent, the researcher will fill in an electronic copy of the consent form and send a signed copy to the participant.

Interviews will be audio-recorded on an encrypted device. Audio recordings will be kept until the end of the study for audit purposes. Reflexive notes will be made during and after the interviews. It is anticipated that patient interviews will last approximately 60 minutes. Due to the nature of their clinical role we anticipate that HCPs may be busy and unable to offer the same length of time therefore, we anticipate HCP interviews will last around 30 minutes.

*HCP topic guide*

- Clinicians will be asked about their current experiences of managing and treating OHSS, including discussion of local protocols.
- During the interview clinicians will be presented with examples of the proposed treatment protocols (emailed to them if necessary) and asked for their views.
- Clinicians will be asked about the planned RCTs, and potential barriers and facilitators to running it in their centre.

*Patient topic guide*

- Sociodemographic information will be gathered at the beginning of the interview in order to report the diversity of the sample.
- Interviews will include discussion of the woman's wider experiences of OHSS, and the treatment they received for it.

- Examples of the proposed treatment protocols will be presented in plain English and women will be asked for their views about them. These will be emailed if necessary.
- Women will be given information about the proposed RCTs and asked about their views e.g. willingness to be randomised, and how to ensure acceptability and feasibility from their perspectives.

**Data Analysis:**

Interviews will be transcribed and anonymised. The qualitative researchers will undertake framework analysis [20]. They will read the transcripts, identify a coding frame, apply it to each transcript and then consider themes and relationships between them. Analysis will be an iterative process so that after a few interviews the findings will be fed back to the research team for the wider study and consideration will be given to changing the treatment protocols or aspects of the RCT procedures. Updated treatment protocols and topic guides can then be used in later interviews.

**Anticipated Impact and Dissemination**

The findings from this qualitative study will be fed back to clinicians as part of a consensus event in order to confirm treatment protocols. Very little research has been undertaken on women's experiences of having OHSS [21] and we will publish a journal article about this. The work may also be presented at conferences and within other journal articles.

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## Appendix A – Patient Recruitment Process Flow Diagrams

1

- The site recruiting HCP (research nurse/midwife/Dr/clinic nurse) will identify patients from medical records, through outpatient clinic or through other clinic visits.

2

- The HCP will make first contact with the patient giving a brief introduction to the study and to ask if they are interested in receiving further information. Contact may be by email, phone or letter. If by email or letter the HCP may follow up with a phone call.

3

- If the patient is interested the HCP will post or email full information to the patient including PIS, response card (with FREEPOST envelope if by post) and the research team's contact details.

4

- Patients indicate their consent to participate by returning a response card by email or in a FREEPOST envelope that will be included in their information pack, or by contacting the research team directly.

## Information for HCP recruiting women from medical records

Recruiting HCP identifies potential participant from medical records

Recruiting HCP contacts potential participant via post / email directly sending a pack that includes

- Introductory letter/email from HCP (document I)
- Participant information sheet
- Response card (and FREEPOST envelope if by post)

Recruiting HCP contacts potential participant over the phone with initial information about study and asks

- if they would like further information and best route (email or post) to send information

Recruiting HCP sends information via email or post including:

- Introductory letter from HCP (document J)
- PIS Form
- Response card (and FREEPOST envelope if by post)

## Information for HCP recruiting women in clinic

Recruiting HCP identifies potential participants from clinic

Recruiting HCP gives brief introduction to study and asks if the patient would be interested in further information.

If patient is interested then recruiting HCP to give or email patient:

- Introductory letter (document J)
- Participant information sheet
- Response card (and FREEPOST envelope if by in person)