Article:
Metwally, M., Ridsdale, K., Pye, C. et al. (2026) Outpatient paracentesis for Ovarian Hyperstimulation Syndrome: STOP-OHSS feasibility study and RCT Synopsis. Health Technology Assessment, 30 (42). pp. 1-34. ISSN: 1366-5278

https://doi.org/10.3310/gjmm1724

NIHR | National Institute for Health and Care Research

Health Technology Assessment

Check for updates

Synopsis

Outpatient paracentesis for Ovarian Hyperstimulation Syndrome: STOP-OHSS feasibility study and RCT Synopsis

Mostafa Metwally,[1] Katie Ridsdale,[1*] Clare Pye,[2] Munya Dimairo,[1] Amy Barr,[3] Ying Cheong,[4] Lauren Desoysa,[1] Sarah Drabble,[1] Andrew Drakeley,[5] Isaac Evbuomwan,[6] Laura Flight,[1] Jennifer Hannington,[7] Jane Hughes,[1] Anju Keetharuth,[1] Amanda Loban,[1] Elizabeth Lumley,[1] Raj Mathur,[8] Kirsty McKendrick,[1] Cara Mooney,[1] Alicia O'Cathain,[1] Eloise Pyper, Rich Simmonds,[1] Liz Taylor,[2] Jessica Wright,[1] Siqi Wu,[1] Tracey Young[1] and David White[1]

[1]Sheffield Centre for Health and Related Research, The University of Sheffield, Sheffield, UK
[2]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[3]National Institute of Health and Care Excellence, London, UK
[4]School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK
[5]Hewitt Fertility Centre, Liverpool Women's NHS Foundation Trust, Liverpool, UK
[6]Gateshead Health NHS Foundation Trust, Gateshead, UK
[7]Patient and Public Involvement
[8]Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust, Manchester, UK

*Corresponding author k.ridsdale@sheffield.ac.uk

Published May 2026
DOI: 10.3310/GJMM1724
Volume 30 • Issue 42

Abstract

Background: Ovarian hyperstimulation syndrome is a potentially serious complication of fertility treatments. Standard care often involves monitoring, then hospitalisation for severe cases. Some evidence suggests early outpatient paracentesis may prevent hospitalisation, but adequately powered randomised trials are lacking.

Objectives: To establish the clinical and cost-effectiveness, safety and acceptability of early active outpatient management for moderate or severe ovarian hyperstimulation syndrome.

Design and methods: A pragmatic, parallel, open-label, multicentre, superiority, adaptive, group sequential randomised controlled trial with an internal pilot was planned. The study included preliminary qualitative work and a post-trial survey. The main trial recruited participants with moderate or severe, early or late ovarian hyperstimulation syndrome from UK fertility clinics. Participants were randomised 1 : 1 to receive either outpatient paracentesis or usual care (conservative management). The primary outcome was ovarian hyperstimulation syndrome-related hospital admission within 28 days.

Results: The trial was terminated early due to poor recruitment. Only 8 participants were randomised (5 to conservative management, 3 to outpatient paracentesis) across 3 of 9 opened sites, compared to the planned 224 participants. All eight had moderate ovarian hyperstimulation syndrome at baseline. Two participants were hospitalised for ovarian hyperstimulation syndrome-related reasons (one from each group). Six participants' symptoms resolved during follow-up, while two had unknown outcomes. There were no reported serious adverse events caused by the intervention. The post-trial survey of 16 fertility centres found increased use of preventive measures like freeze-all cycles, antagonist protocols and gonadotropin-releasing hormone trigger, during and after the SARS-CoV-2 (COVID-19) pandemic.

This synopsis should be referenced as follows:
Metwally M, Ridsdale K, Pye C, Dimairo M, Barr A, Cheong Y, *et al*. Outpatient paracentesis for Ovarian Hyperstimulation Syndrome: STOP-OHSS feasibility study and RCT Synopsis. *Health Technol Assess* 2026;**30**(42):1–34. https://doi.org/10.3310/GJMM1724

Limitations: The small sample size precludes drawing any definitive conclusions about effectiveness, safety or cost-effectiveness. The study was severely impacted by the COVID-19 pandemic, affecting site set-up and recruitment, and changes in clinical practice during the pandemic may have reduced ovarian hyperstimulation syndrome cases.
Conclusions: No definitive clinical conclusions can be drawn from this study about the effectiveness of outpatient management compared to conservative management. The pandemic prompted lasting modifications in ovarian hyperstimulation syndrome prevention strategies at many fertility clinics.
Future work: Given the observed low incidence rates of ovarian hyperstimulation syndrome and challenges in recruitment, future research may need to consider alternative study designs in observational settings rather than randomised trials that reflect the changing reality of clinical management and prevention of ovarian hyperstimulation syndrome, particularly following the recent COVID pandemic. Additionally, the research community should reflect on strategies to improve trial resilience and adaptability in the face of major disruptions like pandemics.
Funding: This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number NIHR128137.
A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/GJMM1724.

Introduction

This report describes the efforts carried out by the STOP-OHSS (Shaping and Trialling Outpatient Protocols for Ovarian HyperStimulation Syndrome) project, to investigate the clinical and cost-effectiveness, safety and acceptability of early active outpatient management of ovarian hyperstimulation syndrome (OHSS). This randomised controlled trial (RCT), with a feasibility study, was a response to a call by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme.

The work carried out for this study is broken down into:

- Phase 1, preliminary feasibility work: Retrospective Review, Qualitative Interviews, and Consensus Development Panel.
- Phase 2: RCT.
- Phase 3: Post-trial survey of centres on their clinical practice.

Due to slow recruitment, the RCT was closed early, after the randomisation of eight participants.

Rationale for research and background

Ovarian hyperstimulation syndrome is a common side effect of Assisted Reproductive Technology, including in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) and intrauterine insemination. Fluid builds in the ovaries and can leak into body cavities. The Royal College of Obstetricians and Gynaecologists divide OHSS into mild, moderate, severe or critical categories.[1] In critical cases, patients can suffer from respiratory distress, thrombosis, disturbed renal and liver functions and, in rare cases, death.[2] OHSS can be further divided into two categories: early OHSS and late OHSS. Early OHSS typically occurs within 7 days after the final dose of the hormone human chorionic gonadotropin (hCG), which is administered as part of the ovarian stimulation treatment. Late OHSS usually occurs 10 days or more after hCG administration and is caused by the body's own production of hCG due to a resulting pregnancy. Late OHSS is more likely to be severe in nature.[3]

In the UK, standard treatment focuses on monitoring the condition, and only intervening if it reaches a severe state, requiring hospitalisation, and inpatient management, which can include drainage of ascitic fluid by a procedure called paracentesis. Moderate and severe OHSS occur in up to 8% of patients undergoing IVF.[1] There is some evidence that early paracentesis can prevent hospitalisation, that this can be carried out safely and effectively in an outpatient setting, and can be more cost-effective than less active management and inpatient admission.[4–10] Likewise, early administration of gonadotropin-releasing hormone (GnRH) antagonists has shown promise in preventing hospitalisation.[11–16] However, there is a lack of adequately powered RCTs investigating these treatments.

This study initially intended to provide robust evidence on whether earlier outpatient paracentesis (OP), or administration of GnRH antagonists in the outpatient setting, could safely prevent escalation of symptoms and hospitalisation of patients with moderate or severe OHSS, with separate trials in early and late OHSS planned. However, following phase 1 of the project, concerns about recruitment feasibility necessitated a change in scope and simplification of the original design, resulting in a single RCT assessing OP verses usual care (UC) (conservative management) in both early and late OHSS. The original and amended design are illustrated in *Appendix 1* and further described in the phase 1 results and discussion below.

Aims and objectives

The overall aim of STOP-OHSS was to establish the clinical and cost-effectiveness, safety and acceptability of early active outpatient intervention for patients with moderate or severe OHSS. There were three phases.

Phase 1 consisted of three components:

- Retrospective review: the aim was to conduct a robust review of patient records at our collaborating centres to inform the design of the STOP-OHSS clinical trial/s and to assess the feasibility of conducting the trial/s.
- Qualitative study: this aimed to explore the acceptability and feasibility, to fertility patients and healthcare professionals (HCPs), of early active outpatient intervention for moderate or severe OHSS occurring at an early or late stage.
- Consensus development panel: aimed to confirm consensus-driven treatment protocols for earlier active outpatient management of OHSS for testing in the planned RCT/s.

The components which addressed the preliminary work objectives are displayed in *Table 1*.

Phase 2 was the RCT. The primary objective was to establish whether OP reduces the rate of OHSS-related hospital admissions in those presenting with moderate or severe OHSS compared with conservative management. Secondary objectives were to establish: whether OP prevents the escalation of OHSS severity; whether OP reduces the time taken for OHSS symptoms to resolve; the safety of OP as an active intervention for moderate or severe OHSS; whether OP would improve patient satisfaction and quality of life; whether OP is cost-effective by examining healthcare resource use and patient costs. An additional objective was to facilitate the feasibility of conducting the RCT by identifying problems with the conduct of the RCT during an internal pilot.

Phase 3 was the post-trial survey. This aimed to examine if and how clinical practice at UK fertility units changed to reduce OHSS-related hospitalisations during and after the COVID-19 pandemic, and to provide insight into the consistency of approaches nationally and help inform future practice.

Methods

Phase 1: preliminary work

Retrospective review

NHS Fertility centres across the UK, for which the research team had contact details, were asked for their UC protocols and standard operating procedures (SOPs) regarding OHSS. Information was extracted and summarised using NVIVO Version 12 (Lumivero. Denver, CO, USA]

TABLE 1 Objectives addressed by different components in phase 1 (preliminary work) of the STOP-OHSS study

Objective specified in application	Qualitative	Consensus	Review
(a) Paracentesis: when and how often to be undertaken as early treatment; acceptability to patients of being undertaken as outpatient in practice	x	x	
(b) GnRH antagonists (early population only): timing and length of administration	x	x	
(c) Monitoring: acceptability to patients and feasibility of home monitoring and regular self-report of symptoms; frequency, measures and methods used (e.g. urine output, abdominal girth); frequency of clinic attendance	x	x	
(d) Information and training provided to participants on self-monitoring and education regarding rehydration	x	x	
(e) HCP confidence in delivering the interventions	x		
(f) Acceptability of randomisation	x		
(g) Acceptability and feasibility of frequent EuroQol-5 Dimensions, five-level version (EQ-5D-5L) administration, including in	x		
(h) Criteria for hospitalisation	x	x	
(i) Current UC across	x		x
(j) Incidence and hospitalisation rates of patients who would be eligible for both RCTs			x

based on the following: OHSS definitions, identification/monitoring at risk patients, diagnosis of OHSS, prevention, outpatient management, criteria for admission, resolution of symptoms. Sites were also requested to search for patients who may have had moderate or severe OHSS that occurred over a 1-year period between 1 March 2019 and 29 February 2020 – a period prior to the COVID-19 outbreak in the UK. This included anyone undergoing IVF with or without ICSI or intrauterine insemination. Sites were asked to add information on these resulting patients to a spreadsheet. Suggested search terms were provided, and sites were asked to include every patient revealed by the searches, even if OHSS was not stated in the notes. Sites were instructed not to use 'hospital admission' as a search criterion, to prevent overestimation of the true hospitalisation rate (the primary outcome of the planned RCT). Requested information included: total number of cycles for all patients receiving fertility treatment over the time period, total number of patients, IVF cycle details (trigger date, embryo transfer, use of GnRH); OHSS summary (symptoms, hospitalisation), full blood count (FBC) results, outpatient treatment and hospitalisation details. A formula was developed to highlight whether each patient would have met the exclusion criteria, and to count the features of Mild, Moderate, Severe and Critical OHSS reported for each patient, to provide an estimation of their OHSS severity.

Qualitative study

Concurrently, qualitative semistructured interviews were conducted with HCPs (n = 8) and fertility patients who had previously experienced OHSS (n = 10) across six UK fertility clinics. Interviews explored experiences of OHSS, views on the proposed treatment protocols, and potential barriers and facilitators to a RCT evaluating these treatments. More detail on these methods can be found in Lumley *et al.* (2023)[17] and the qualitative paper under review.[18]

Consensus development panel

The above work fed into development of documents which were then taken to a Consensus Development Panel. A day-long virtual meeting was held on 22 April 2021 with HCPs (doctors, nurses and research nurses or midwives) and a patient representative. HCPs were sampled from a mix of NHS and private fertility centres with different experience, including those who were already undertaking OP and those with no experience of this procedure. Based on the recommended sample size for Consensus Development Panels,[19] the aim was to include 8–12 HCPs and a patient representative. Invitations were sent to six nurses, seven doctors and a patient representative. One nurse and 2 doctors were unable to attend, therefore there were 11 participants, with representation from 9 diverse centres, including a private centre, and a centre where OP was undertaken. The day was separated into different parts, with discussions focusing on five documents (see *Report Supplementary Material 1*): STOP-OHSS treatment protocol; OP treatment protocol; administration of GnRH antagonists treatment protocol; criteria for the secondary outcome measurement of hospitalisation of patients; patient diary (for patient self-monitoring). Detailed documentation was sent to participants beforehand, with specific questions relating to areas of uncertainty. The day was facilitated by the chief investigator and qualitative lead in the morning, and senior research nurse and qualitative lead in the afternoon, ensuring a combination of clinical leadership and consensus exercise expertise.

Phase 2: randomised controlled trial

The main trial was a pragmatic, parallel, open-label, multicentre, superiority, adaptive, group sequential,

TABLE 2 Status of results papers from the project synthesised in this report

Component	Title	Status	Reference
Protocol	Outpatient paracentesis for the management of ovarian hyperstimulation syndrome: study protocol for the STOP-OHSS RCT[20]	Published in *BMJ Open*	https://doi.org/10.1136/bmjopen-2023-076434
Qualitative interviews	Managing ovarian hyperstimulation syndrome: a qualitative interview study with women and healthcare professionals[17]	Published in *Journal of Clinical Nursing*	https://doi.org/10.1111/jocn.16701
Qualitative interviews	Views on outpatient paracentesis and GnRH antagonists for ovarian hyperstimulation syndrome: a qualitative study of patients and healthcare professionals[18]	Published in *Health Technology Assessment*	https://doi.org/10.3310/GJMM2923
RCT and post-trial survey	Ovarian hyperstimulation syndrome: the STOP-OHSS RCT of outpatient paracentesis and survey on preventive practices[21]	Pre-print published on *medRxiv*	https://doi.org/10.1101/2025.07.18.25331764

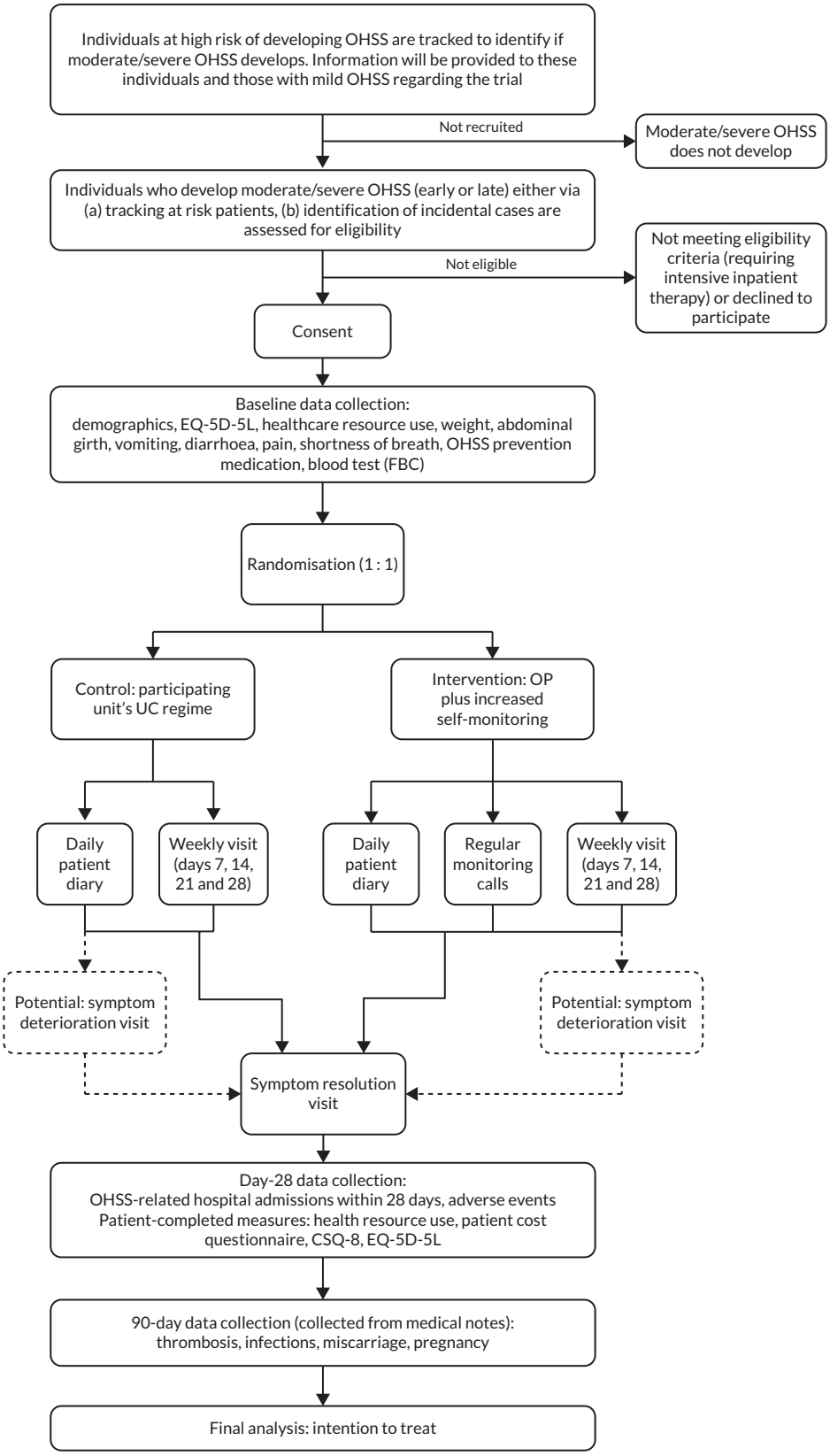

FIGURE 1 The STOP-OHSS RCT flow diagram. CSQ-8, Client Satisfaction Questionnaire 8.; EQ-5D-5L, EuroQol-5 Dimensions, five-level version.

confirmatory RCT with an internal pilot (after 15 of 31 months of recruitment, to assess feasibility aspects) (*Figure 1*). Full details are published in our protocol paper,[20] and the trial protocol in the International Standard Randomised Controlled Trial Number (ISRCTN) registry.[22] The statistical analysis plan (SAP) was reviewed and

approved by the Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC), and uploaded to the University of Sheffield data repository ORDA, before data collection was completed and analysis had started.[23]

The trial aimed to recruit 224 patients. Patients were eligible if they experienced moderate or severe, early or late OHSS, and were able and willing to attend the monitoring calls and follow-up appointments and undertake self-monitoring at home. Patients were excluded from participation if they had: significant pain or vomiting requiring hospitalisation; pulmonary embolism; a condition severe enough to warrant admission to a high-dependency care unit; concurrent medical conditions requiring immediate inpatient management; been previously been randomised and involved in the trial; been involved in other trials involving ovarian stimulation or ovarian response. Participants were randomised (1 : 1) by the site using a centralised web-based system (SCRAM) to receive either conservative management or OP with increased monitoring. The randomisation sequence was computer-generated using random permuted blocks of sizes 2 and 4, with stratification by recruiting site and OHSS severity. The trial statistician generated the randomisation sequence but did not have access to the generated sequence and was blinded to participant randomisation until analysis.[21]

All participants were asked to complete a daily diary of their symptoms, which was initially provided in paper format, then later via Research Electronic Data Capture (REDCap).[24] This was to collect their weight, abdominal girth, diarrhoea, vomiting, pain, shortness of breath, fluid input and urine output.

After randomisation, participants allocated to the intervention arm had OP as soon as clinically possible. The study sites were recommended to adhere to their established local protocols for performing paracentesis, whether through an abdominal or vaginal approach. The procedure was carried out by an appropriately trained physician, advanced practice nurse or radiologist from the fertility, gynaecology or radiology department. Site staff were asked to carry out increased monitoring of these participants. This involved daily monitoring at first (either in a clinic or over the phone), which was advised to be reduced based on clinical need. The clinical team reviewed the daily diary data online (or over the phone if paper diaries) to inform further management and whether to perform further OP.

Patients allocated to the control arm did not have paracentesis performed in an outpatient setting. If it was already part of their UC, sites were asked not to conduct paracentesis in an outpatient setting for participants allocated to the control group. These patients were monitored by their clinical team as per the UC at that site. The daily diary data were sent directly to Clinical Trials Research Unit (CTRU) to input to the database, for purposes of assessing the progression of the disease.

Data were also collected on the preventative measures used at the fertility centres. No other preventative measures were prohibited.[21] All participants were monitored weekly until either their symptoms had resolved, or until 28 days had passed without symptom resolution. All participants were asked to attend weekly follow-up appointments (in clinic or remotely) until their symptoms had resolved. Data were also collected during hospitalisation where appropriate. At 28 days post randomisation, site staff assessed whether any OHSS-related hospital admissions had occurred, and the central research team sent participants questionnaires on: health resource use, patient cost, client satisfaction, EuroQol-5 Dimensions, five-level version (EQ-5D-5L), adverse events. Follow-up data were collected from medical notes at day 90 post randomisation. The initial trial design planned to collect pregnancy and birth outcome data in patients who were pregnant after 13.5 months. An interim and a full cost–utility analyses (CUAs) were planned.

Unfortunately, the study was closed early due to poor recruitment; therefore, follow-up data were only collected up to the 28-day post-randomisation time point, at which the primary outcome of hospitalisation was collected, and the 90-day post-randomisation collection point. Data were not collected at 13.5 months.

There was also a second qualitative study planned, focused on exploring and improving recruitment and informed consent procedures. We planned to interview staff who had attempted to recruit at least three patients, as well as record recruitment sessions. The delays in opening sites, and the difficulties staff had identifying patients with OHSS in the first place, prevented this work progressing to timetable. Data collection was in the process of being arranged but had not yet commenced when the decision was made to terminate the RCT.

Phase 3: post-trial survey

Once the study had been terminated, we conducted a survey of sites to investigate any changes in clinical practice, particularly as a result of the COVID-19 pandemic, which may have impacted the incidence of OHSS. The survey was sent to all 10 sites that were open to recruitment to the main trial, and a further 22 fertility centres across the

UK were invited to participate (all centres for which the research team could obtain contact details). The survey questions can be found in *Appendix 2*. Questions were mostly closed with multiple-choice answers; there were a small number of open questions with a free-text box to provide more detail. Respondents were encouraged, but not required, to answer all questions.

Results summary

In addition to the published trial protocol, three results papers have been published (see *Table 2*). The findings described in those papers are summarised in this section.

Phase 1

Retrospective review

Twelve fertility centres submitted their SOPs to the study team, which assisted with developing the study protocol (see *Appendix 3*). However, only seven centres completed the requested spreadsheets containing anonymised patient records, and only six were able to provide data on mild/moderate OHSS cases. *Appendix 1* summarises the estimated incidence and hospitalisation rates compared to the assumptions originally used to design the RCTs. The data revealed challenges in executing the originally conceived RCT due to a lower-than-anticipated prevalence of early OHSS. Conversely, there was a higher-than-expected incidence of late OHSS. This resulted in a decision to simplify the original trial design, combining the originally planned early OHSS and late OHSS RCTs into one trial and removing the GnRH antagonist arm, focusing solely on an evaluation of OP in both early and late OHSS. This change was approved by the TSC and funder.

Qualitative study

Qualitative interviews were undertaken with 10 patients who had experienced OHSS, and 8 HCPs. Both HCPs and patients expressed overall support for the proposed RCTs. Patients welcomed the concepts of self-monitoring symptoms and avoiding hospitalisation when possible; some dissatisfaction was voiced regarding the current lack of 'active treatment' and lack of monitoring they received when undergoing fertility treatments or having OHSS. Several concerns were raised regarding the STOP-OHSS study design. Perceived risks of OP and feasibility issues for delivering this procedure in outpatient settings were cited as potential barriers. Recruitment of patients with late-stage OHSS was also anticipated to be difficult. Furthermore, defining the distinction between moderate and severe OHSS requiring intervention proved challenging. This formative work informed the development of our recruitment protocols. In addition, HCPs reported a shift to more preventive practices due to the COVID-19 pandemic. More information can be found in the separate qualitative study publication (see *Table 2*).

Consensus Development Panel

In general, the participants were satisfied with the content of the documents and treatment protocols, with the exception of the patient diary. They discussed the changes necessary to make the study and treatment protocols feasible and acceptable. For example, there were concerns regarding the patient diary: clarifying the data required, optimising measurement methods and ensuring brevity. For the study protocol, participants emphasised careful consideration of exclusion criteria, virtual visits, standardising care across sites, and highlighted potential recruitment challenges (see *Appendix 4* for more details).

Phase 2: randomised controlled trial

The trial was closed early due to poor recruitment. Though the target sample size was 224, only 8 participants were randomised across 3 of the 9 sites which were opened to recruitment, between 5 November 2022 and 25 May 2023 (*Figure 2*). Five were randomised to conservative management and three to OP. All eight participants had moderate OHSS at baseline; five had early OHSS, and the remaining three had late OHSS.

Hospitalisation and ovarian hyperstimulation syndrome progression

Two participants were hospitalised for OHSS-related reasons. One of these had been randomised to conservative management, and was hospitalised 'for immediate rehydration and progression from severe to critical OHSS' for a duration of 89.3 hours. The other had been randomised to OP, but instead was hospitalised 'for pain relief, nausea, shortness of breath, vomiting, and abdominal distention', and received inpatient paracentesis, with a hospitalisation duration of approximately 246 hours. Six participants' symptoms resolved during the 28-day follow-up period, while two participants had unknown outcomes as the data could not be collected. Three participants in the conservative management group were known to have resolved their symptoms by days 9, 12 and 14, respectively; while three participants in the OP group had their OHSS symptoms resolved by days 7, 21 and 28, respectively.

Patient satisfaction

Only half of the participants (three allocated to conservative management vs. one allocated to OP) completed the Client Satisfaction Questionnaire 8[25] at 28 days post randomisation. Only one participant reported a low

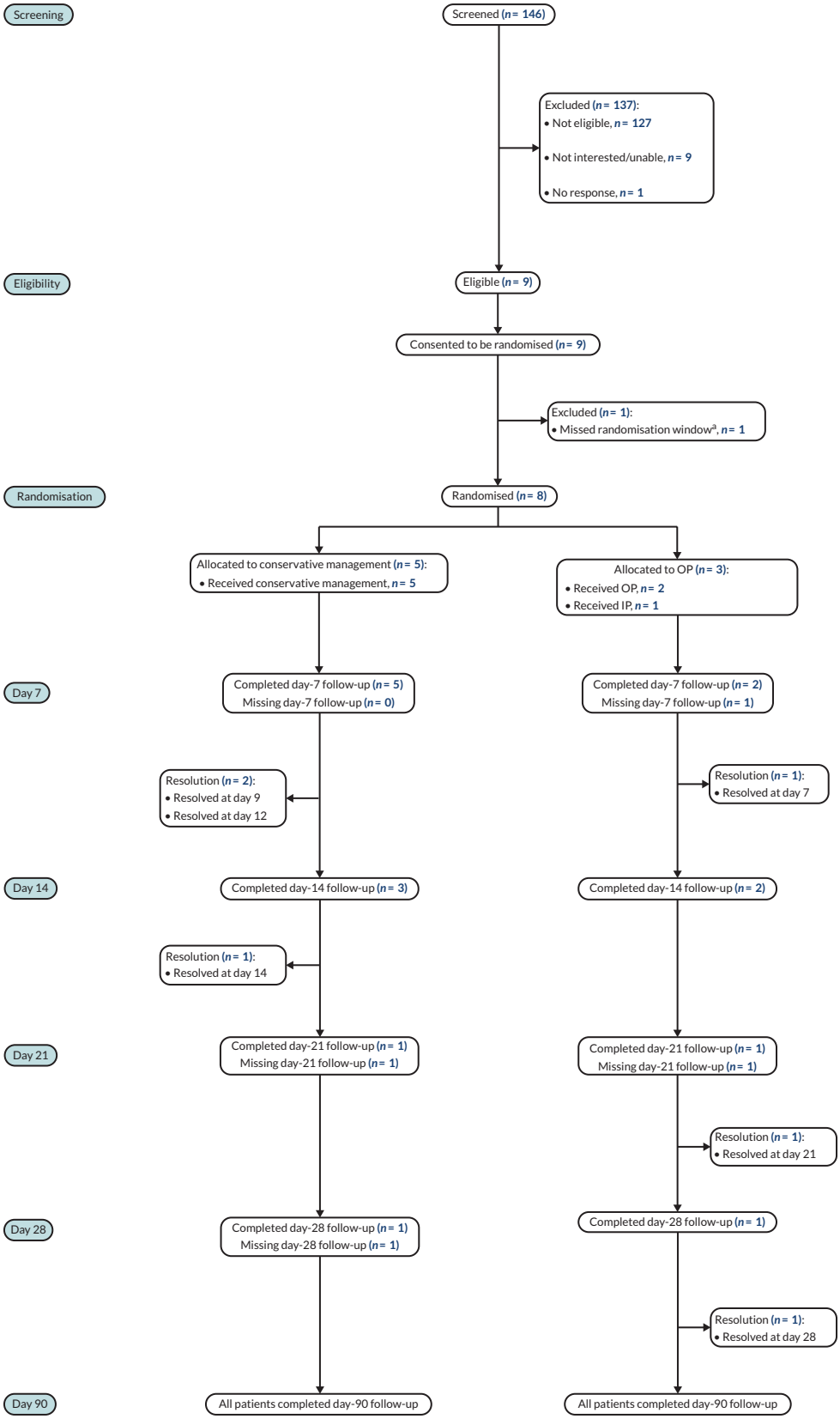

FIGURE 2 Flow of participants. a, There was one incident where a site was unsure if a patient could be randomised based on when their blood test was taken, and, unfortunately, was therefore not randomised. IP, inpatient paracentesis.

satisfaction score of 15; this participant was randomised to conservative management. The other three were extremely satisfied with scores of 31, 32 and 32.

Safety

Six adverse events (including repeated events) were reported by participants; two randomised to conservative

management, and four randomised to OP. Only one unexpected serious adverse event of moderate intensity was reported by a participant randomised to OP; this was viewed as due to pregnancy and not related to the intervention. No participants experienced thrombosis or embolism within 90 days of randomisation. Only one participant who was randomised to OP reported an infection that did not require hospitalisation on day 90.

Health economics

Given the early closure of the trial with only eight participants randomised, a CUA could not be carried out. Total costs were calculated, but numbers were too low for averages to be meaningful or for significance between groups to be assessed (see *Appendix 5*).

Phase 3: post-trial survey

Survey responses were received from the 16 sites in total. Ten of these sites were already open to the STOP-OHSS RCT, and six were new sites. The survey was completed by the principle investigator in open STOP-OHSS sites, or an equivalent consultant at new sites. One site was private, and the remainder were NHS trusts. Sites were distributed across Northern England, the Midlands, Southern England and Scotland.

Thirty-one per cent (n = 5) of respondents believed that the incidence of moderate and severe OHSS had decreased during/after the COVID-19 pandemic, whereas the remaining 11 respondents believed it did not change. However, sites reported that a number of changes in preventive practices were made during the COVID-19 pandemic and maintained after the pandemic. Almost all (91%, n = 10) sites that routinely undertake freeze-all cycles increased their elective freeze rate from before to after the pandemic. The increase ranged from 0.6% to 20%. Fifty-three per cent (n = 8) of sites reported that they increased their use of the antagonist protocol during the pandemic, and six maintained this after the pandemic. Additionally, 53% (n = 8) of sites increased their use of GnRH trigger and maintained this after the pandemic. A further two sites increased their single embryo transfer rate, and one increased use of cabergoline. More information can be found in the separate study results paper (see *Table 2*).

Discussion/interpretation

Phase 1: preliminary work

Retrospective review

The retrospective review obtained usable data from only 6 of the planned 20 sites, reportedly due to sites struggling with staff capacity during the COVID-19 pandemic. From the information received, we found a lower-than-expected number of patients having presented with early OHSS. The original plan for the project was for two RCTs – one in early OHSS and the other in late OHSS – with a GnRH antagonist arm included in the early OHSS RCT only (due to the drug's potential risks in pregnant people with late OHSS). Consequently, the study was granted approval by the TSC and funder to simplify this original design, consolidating the two trials into a single trial investigating the effectiveness of OP for patients with early or late OHSS, thereby enhancing the feasibility of the project. We anticipated the disease incidence would be large enough for the revised study to be feasible.

Qualitative study

The qualitative study identified facilitators and barriers for the two interventions under consideration. Identifying support for, and concerns about, the proposed treatments and RCTs offered the opportunity to address concerns when refining the treatment protocols and RCT procedures. The findings were fed back to the research team during data collection. Team members were able to consider changes to the treatment protocols ready for discussion at the Consensus Development Panel, as well as changes to the proposed RCT procedures and RCT design. It was also one of the first studies to explore HCP and women's experiences of the management of OHSS. However, fewer participants were recruited than planned due to delays caused by the COVID-19 pandemic, and our sample was biased towards women who had experienced early OHSS despite multiple actions taken to recruit women who had experienced late OHSS. This could be related to the fact that those who had experienced late OHSS would have been pregnant.

Consensus Development Panel

A key strength of the consensus exercise was the diverse range of experts who attended the Consensus Development Panel and who engaged fully in discussion. A limitation was that 6 out of 11 clinicians left the meeting before the hospitalisation outcome was discussed. This limitation was addressed through further discussion at the following Trial Management Group (TMG), where doctors from four clinical centres were present.

Phase 2: randomised controlled trial

The trial was terminated early for poor recruitment after recruiting only 8 participants of the planned 224. The results presented are only descriptive due to the small sample size, and therefore, no definitive conclusions can be drawn about the effectiveness and safety of OP compared to conservative management. However, based on these eight cases of moderate OHSS, there are preliminary

indications that OP can safely be used to manage OHSS patients, although its effect on outcomes, such as OHSS-related hospitalisation and time to symptom resolution as well as cost implications, is still unclear.

Phase 3: post-trial survey

While approximately one-third of respondents perceived a decrease in moderate and severe OHSS incidence due to the COVID-19 pandemic, most suspected no change. Notable shifts in clinical practices included: increased elective freeze-all cycles in almost all sites that conduct them, greater use of antagonist protocols in approximately half of sites and increased use of GnRH trigger in approximately half of sites. These findings suggest that the pandemic prompted lasting modifications in OHSS prevention strategies at many fertility clinics.

A disadvantage of the survey is that the questions were largely subjective and based on the opinion of the staff member who answered. Although we received responses from 16 centres, the response rate to the survey would ideally have been higher, with 107 Human Fertilisation and Embryology Authority licensed fertility centres across the UK in 2022–3.[26]

Reflections and challenges

The study encountered significant challenges in establishing research sites and recruiting participants, in large part due to the COVID-19 pandemic. The pandemic led to major obstacles in engaging and opening new sites, as research and development (R&D) departments initially prioritised COVID-19-related studies and urgent public health work, then subsequently shifted their focus to commercial projects. This resulted in a backlog of studies, causing longer wait times for the STOP-OHSS study to be reviewed. Clinical and research staff had limited availability to attend training sessions or confirm their capacity and capability to conduct the RCT. This was exacerbated by staff on sick leave, continuous redeployment of staff to clinical areas or vaccination efforts, and a nationwide shortage of nursing and midwifery staff with the necessary skills and knowledge in Reproductive Health and Childbirth to successfully recruit and manage patients. Additionally, research staff were instructed to use up their annual leave over the summer, further impacting their availability.

The issues with establishing sites and recruiting participants were exacerbated by the Department of Health and Social Care Research Reset programme, which was developed to review whether studies would deliver their outcomes to free up research capacity. However, it was felt that this programme did place some further strain on R&D departments and the research team's capacity at the CTRU. The inclusion of the study on the reset list also made it riskier for sites to set up, and due to prolonged decision-making processes, the research team was unable to inform sites about the study's continuity, diminishing their enthusiasm for set-up and recruitment, for what may be a wasted effort.

Poor recruitment was compounded by the fact that the STOP-OHSS trial focused on a relatively rare condition. In the qualitative work, HCPs reported that practices were changing to be more preventive due to the COVID-19 pandemic. This may have resulted in a perceived lower incidence of OHSS. The post-trial survey provides insight into how fertility practices, particularly preventive measures for OHSS, changed across UK centres in response to the COVID-19 pandemic, with many centres adopting more conservative approaches that appear to have been largely maintained after the pandemic. The pre-trial work had a strong focus on determining the feasibility of recruitment rates for the RCT; however, this work was also impacted by the COVID-19 pandemic, with only six sites able to provide detailed data for the retrospective review – additionally, data were collected for the 1-year period prior to the start of the pandemic, so any effect of the pandemic on OHSS incidence rates will not have been reflected in the data – nevertheless, this work resulted in a simplification of the trial design and overall reduction of the target sample size.

We believe that having to conduct activities such as site initiation visits and monitoring remotely, due to the pandemic, resulted in issues with engagement and memorability. An in-person investigator meeting, initially planned for 22 April 2020, had to be cancelled. The investigator meeting was rescheduled for 13 October 2022. There was in-person representation from 19 NHS trusts nationally, the Fertility Network and a public representative. Principal investigators (PIs), associate PIs, research nurses and midwives from open sites and prospective sites attended. The purpose of the meeting was to generate discussion among experienced clinicians, disseminate the centralised support strategy and raise the profile of the trial to improve recruitment and encourage other sites to take part. A feedback survey received 10 responses, with an overall average rated usefulness of presentations for sites already taking part of 9.5, and for sites considering taking part of 9.2. Nine said they would attend again, whereas one said maybe.

We do not believe that any other actions could have significantly improved the recruitment rate in this project. The study team made strong efforts to improve site

engagement and recruitment. To mitigate site set-up issues, a clear and thorough 'site opening process' was implemented, wherein local information packs and amendment packs were clearly shared, earning compliments from R&D departments. All site initiation visits were conducted remotely, often more than once per site and with recordings shared to allow flexibility for all staff to attend or view these. The central team were readily available to aid site staff. The team devised a recruitment strategy to provide centralised research nursing support to all participating sites in the trial, which was ultimately available out of hours and at weekends (further discussed in Impact and learning).

The team also sent regular e-mails highlighting the importance of patient recruitment, newsletters, and held monthly nurse meetings. Central team members attended several conferences to discuss the trial and make new connections. In attempts to improve recruitment, the team developed a recruitment video that clearly explained the trial for use at sites when introducing the studies to potential participants. The team were also beginning to make progress engaging with private centres to open to recruitment.

Other challenges faced by the project included the difficulty in acquiring daily diary data, problems conducting follow-ups over weekends and adjudication of some outcomes. The feasibility of these processes should be given consideration before beginning future projects. These issues are also discussed further under the section 'Impact and learning.

Patient and public involvement

Aim

The goal of patient and public involvement (PPI) in this project was to incorporate the perspectives of those living with and impacted by OHSS and fertility treatment into all phases of the project, from design, to execution, to sharing results. By integrating these views, we aimed to ensure the findings could benefit those affected by OHSS and fertility issues.

Methods and outcomes

Patient and public involvement provided valuable insights throughout the trial, including in developing the funding bid, setting up study procedures and shaping the way in which the qualitative element of the study was undertaken.

A number of study documents were taken to the Reproductive Health Research Public Advisory Panel at Sheffield Teaching Hospitals over the course of the project. This meeting is held regularly and provides a great opportunity to obtain feedback on suggested changes to the project, or advice on patient-facing documents. Changes were made to improve clarity of documents. For example, the qualitative study protocol, and the participant information sheets (PIS), and the RCT treatment protocols were discussed. The panel suggested simplifying PIS, particularly the information about data sharing, to make it more user-friendly. In response to the PPI group comments, the documents were amended to improve readability for a lay audience, and the data-sharing information was rewritten according to Health Research Authority recommendations. The treatment protocols were changed considerably in terms of presentation and the information provided. The PPI group also suggested that the treatment protocols should be split into 'early' and 'late' trial-specific information and that they would benefit from simpler presentation. All revised documents were returned to the PPI group for their final approval before they were submitted for ethical review. PPI members also attended the Consensus Development Panel to help to agree on trial protocols for the main trial. Other new study documents were reviewed by this PPI group throughout the study.

A representative from Fertility Network UK attended TMG meetings. They were involved in all main discussions and decisions; for example, they offered suggestions on recruitment strategies and timing, and advocated for the option of online rather than paper diaries. This representative also spoke at the investigator meeting, sharing quotes from patients affected by OHSS that underscored the importance of this research. The talk was well received, and emphasised the value of PPI engagement in clinical trials overall.

We similarly involved two PPI members in TSC meetings, with support from Fertility Network UK to recruit a new member after losing contact with the first. This PPI member attended the investigator meeting as well, relaying their personal experience of hospitalisation for severe OHSS. They described the painful physical and emotional toll of OHSS on her fertility journey and wider family, and that had this intervention been available during her treatment, they would have welcomed the opportunity to participate in hopes of reducing OHSS progression and avoiding intensive hospital care.

This synopsis was reviewed by two TSC PPI members, and it will be shared with the Advisory Panel after it is published.

Reflections and critical perspective

The valuable insights provided by PPI members helped shape the study procedures, participant materials and treatment protocols in a manner that was more patient-friendly, accessible and relevant. The collaboration with representatives from Fertility Network UK ensured that the study remained grounded in the real-world experiences and needs of patients. The involvement of the Reproductive Health Research Public Advisory Panel at Sheffield Teaching Hospitals provided a structured platform for obtaining feedback and advice on study documents and proposed changes. The inclusion of PPI members in TMG and TSC meetings further allowed for ongoing dialogue and input throughout the trial's progression.

Equality, diversity and inclusion

Of the eight participants randomised to the main trial, one self-identified as Indian and the rest were English/Welsh/Scottish/Northern Irish/British. Previous research has demonstrated that 78% of IVF cycles in the UK are conducted in 'White women'.[27] There is some evidence that Black women are at increased risk of developing OHSS,[28] though other research found no relationship between ethnicity, frequency of IVF cycles and OHSS requiring intensive care unit admission.[29]

The project was deemed unsuitable for participants who did not have a sufficient understanding of English, due to concerns regarding consent, understanding of the trial and completion of daily diaries and questionnaires. It was not considered feasible to translate the patient-facing materials. Although the overall percentage of people who do not speak English or do not speak it well is low in the UK (1.6%), this may have prevented the participation of some members of ethnic minority groups in this project. It is noted that translation of materials is being increasingly considered with the development of new trials.

Impact and learning

As the study was closed early, there were too few participants to determine whether OP was clinically effective, cost-effective, safe and feasible when compared to usual protocols of monitoring and inpatient paracentesis. However, the study did indicate that OP was feasible and safe for the two participants who received it in the trial. Throughout this project, sites were reporting increased confidence with paracentesis in the outpatient department. We believe that this was assisted by our discussions and the investigator meeting. The post-trial survey demonstrated that 3 of the 16 responding sites already carry out paracentesis in the outpatient setting for some patients. Seven were considering implementing this in the future, three were not considering this, and two did not know.

Several lessons were learnt and strategies developed which future projects may wish to consider, discussed below.

Use of a centralised research nursing support team

Inclusion of research nurses as part of the central research team was very helpful to obtain insights and feedback on the practicalities and operationalisation of data collection at sites, and identifying issues with, and other potential pathways for, recruitment.

This centralised support enabled research nurses at Sheffield Teaching Hospitals NHS Foundation Trust to directly contact patients, discuss the studies, obtain informed consent, randomise participants and collect follow-up data if required. Although the impact of this centralised resource was never fully evaluated due to the early closure of the trial, momentum was building, and the unique support offered by the team was a factor in sites' decisions to participate in the study, and a considerable factor in participation from the private sector.

Collection of daily diary data

Participant diary data frequently have issues with completeness. During this project, it was initially intended to capture diary data using printed sheets, which would be completed by participants at home, collected by site staff, posted to CTRU, then input to the database. However, to increase participant response, and reduce burden on site staff, after recruitment of three participants, we implemented an electronic method of capturing these data. This was collected using the REDCap database,[24] which was a different database to the one used to collect the main trial data. Automatic e-mails were sent via REDCap to participants. Participants could then complete their diary online, and the data were uploaded straight to the database. However, the system could have benefited from further PPI involvement and end-user testing. Data existing on two different database systems also caused difficulties during analyses. In future studies, capturing self-reported daily diary data of participants' symptoms over time needs careful thought to encourage completion and to ensure that the daily records are consistent with the date of reporting.

Conducting trials on rare conditions with rapid disease progression

This project was labour-intensive for the first 28 days for both sites and participants. Consideration should be given as to how sites will recruit and follow up participants over weekends. There was one incident where a site was unsure if a patient could be randomised based on when their blood test was taken, and, unfortunately, was therefore not randomised. When studying rare conditions like OHSS, it is important not to miss recruitment opportunities. This incident happened outside of routine clinic hours, and despite the research team's best efforts to develop study management plans facilitating recruitment out of hours, the site was unable to contact the research team. Examples such as this promoted the development and available resource of the centralised research nursing support team to work towards preventing such incidences again.

Outcome adjudication

Independent adjudication is a useful approach to minimise bias in the assessment of subjective outcomes, and this study was designed to have an independent clinical adjudicators panel (involving four clinicians) assess outcomes related to OHSS hospitalisations and time to symptom resolution. Due to the small numbers of participants, adjudication took place at study completion. However, adjudicating time to resolution of symptoms based on self-reported diary data of participants' symptoms (fluid input and output, abdominal girth and body weight) was challenging and ultimately impractical – we found that no agreement or consensus could be reached among adjudicators on the timing of symptom resolution, with substantial variability in their assessment.

This experience highlighted the need for an early piloting phase with mock data to optimise the adjudication process and ensure that all necessary data elements are appropriately collected. However, in the case of symptom resolution, it may not be advisable to attempt this approach in future trials.

Implications for decision-makers

It is not possible to make conclusions about implications for decision-makers.

Research recommendations

Very low incidence rates of OHSS were observed in this study across UK sites. The COVID-19 pandemic and acute consequential changes in practice may have rendered OHSS so rare that it no longer poses a significant risk to women undergoing assisted conception treatment. Therefore, consideration should be given to whether a research question focusing on treatment of OHSS is still a high priority. If it is still considered an important research question, it seems impractical to conduct a fully powered definitive randomised trial. Alternative study designs in observational settings may need to be considered.

We do suggest exploration of establishing a national registry of OHSS cases, likely with involvement from the Human Fertilisation and Embryology Authority. This would allow for more comprehensive data collection on the incidence and clinical implications of OHSS, including the financial burden.

Furthermore, we recommend a study evaluating the use of GnRH antagonist continued from the trigger for 7 days in patients deemed at high risk of OHSS based on their ovarian response. This strategy may help mitigate the risk of OHSS while maintaining treatment efficacy.

Conclusions

Following an exploration of HCPs' and women's experiences of OHSS and with consensus from a panel of experts, a treatment protocol was successfully developed for the delivery of OP in women experiencing moderate or severe OHSS. The subsequent trial was terminated early due to poor recruitment, and therefore, no definitive conclusions can be drawn about the effectiveness, safety and cost-effectiveness of OP compared to conservative management. Our survey findings suggest that the pandemic prompted lasting modifications in OHSS prevention strategies at many fertility clinics. It may, therefore, be impractical to complete a large definitive randomised trial that addresses this research question.

Additional information

CRediT contribution statement

Mostafa Metwally (https://orcid.org/0000-0003-4022-1740): Conceptualisation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – reviewing and editing.

Katie Ridsdale (https://orcid.org/0000-0002-5036-9610): Data curation, Project administration, Software, Visualisation, Writing – original draft, Writing – reviewing and editing.

This synopsis should be referenced as follows:
Metwally M, Ridsdale K, Pye C, Dimairo M, Barr A, Cheong Y, *et al*. Outpatient paracentesis for Ovarian Hyperstimulation Syndrome: STOP-OHSS feasibility study and RCT Synopsis. *Health Technol Assess* 2026;**30**(42):1–34. https://doi.org/10.3310/GJMM1724

Clare Pye (https://orcid.org/0000-0003-4929-7215): Conceptualisation, Funding acquisition, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – reviewing and editing.

Munya Dimairo (https://orcid.org/0000-0002-9311-6920): Conceptualisation, Data curation, Formal analysis, Funding acquisition, Methodology, Software, Supervision, Validation, Visualisation, Writing – original draft, Writing – reviewing and editing.

Amy Barr (https://orcid.org/0000-0002-7990-7451): Project administration, Software, Writing – reviewing and editing.

Ying Cheong (https://orcid.org/0000-0001-7687-4597): Conceptualisation, Funding acquisition, Investigation, Methodology, Writing – reviewing and editing.

Lauren Desoysa (https://orcid.org/0000-0002-6151-836X): Formal analysis, Software, Writing – reviewing and editing.

Sarah Drabble (https://orcid.org/0000-0001-7183-6321): Formal analysis, Investigation, Methodology, Writing – original draft, Writing – reviewing and editing.

Andrew Drakeley (https://orcid.org/0000-0002-8802-4706): Conceptualisation, Funding acquisition, Investigation, Methodology, Writing – reviewing and editing.

Isaac Evbuomwan (https://orcid.org/0000-0003-3194-8614): Investigation, Methodology, Writing – reviewing and editing.

Laura Flight (https://orcid.org/0000-0002-9569-8290): Methodology, Writing – reviewing and editing.

Jennifer Hannington (https://orcid.org/0009-0007-4875-8645): Project administration, Writing – original draft, Writing – reviewing and editing.

Jane Hughes (https://orcid.org/0000-0003-1389-3402): Project administration, Writing – reviewing and editing.

Anju Keetharuth (https://orcid.org/0000-0001-8889-6806): Formal analysis, Writing – reviewing and editing.

Amanda Loban (https://orcid.org/0000-0001-7089-1580): Data curation, Software, Writing – reviewing and editing.

Elizabeth Lumley (https://orcid.org/0000-0002-8962-7568): Formal analysis, Investigation, Methodology, Visualisation, Writing – original draft, Writing – reviewing and editing.

Raj Mathur (https://orcid.org/0000-0002-7550-1817): Conceptualisation, Funding acquisition, Investigation, Methodology, Writing – reviewing and editing.

Kirsty McKendrick (https://orcid.org/0000-0003-0497-3582): Project administration, Writing – reviewing and editing.

Cara Mooney (https://orcid.org/0000-0002-3086-7348): Methodology, Project administration, Software, Writing – reviewing and editing.

Alicia O'Cathain (https://orcid.org/0000-0003-4033-506X): Conceptualisation, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – reviewing and editing.

Eloise Pyper: Project administration, Writing – original draft, Writing – reviewing and editing.

Rich Simmonds (https://orcid.org/0000-0001-5024-8272): Data curation, Project administration, Software, Writing – reviewing and editing.

Liz Taylor (https://orcid.org/0000-0002-4769-3970): Investigation, Software, Writing – reviewing and editing.

Jessica Wright (https://orcid.org/0000-0002-1814-3697): Methodology, Project administration, Software, Writing – reviewing and editing.

Siqi Wu (https://orcid.org/0009-0003-2206-9578): Data curation, Formal analysis, Software, Visualisation, Writing – reviewing and editing.

Tracey Young (https://orcid.org/0000-0001-8467-0471): Conceptualisation, Funding acquisition, Methodology, Supervision, Writing – reviewing and editing.

David White (https://orcid.org/0000-0003-2871-7946): Conceptualisation, Funding acquisition, Methodology, Project administration, Supervision, Visualisation, Writing – original draft, Writing – reviewing and editing.

Acknowledgements

We are very grateful to the patients with OHSS who participated in this study. We are also very thankful to all of the research nurses, midwives, consultants, clinical trials assistants and all other staff at sites who worked hard to identify and recruit patients and carry out this study. We thank the independent TSC, Andrew Horne (Chair), Babak Choordari-Oskooei, Sebastian Hinde, and Ippokratis Sarris, and the independent DMEC, Jane Daniels (Chair), James Wason, Raef Faris, and Howard Thom. We

would also like to extend our sincere thanks to Kate Brian and Anya Sizer from Fertility Network UK, who sat on the TMG; the PPI members who sat on the TSC, and those who attended the Reproductive Health Research Public Advisory Panel at Sheffield Teaching Hospitals.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. De-identified participant data and statistical code will be made available upon reasonable request. Requests should state the data fields required and purpose of the request (ideally with a protocol but, at a minimum, with a research plan). The data dictionary and SAP can also be made available. Requests will be considered on a case-by-case basis, and requestors will be asked to complete a data-sharing agreement with the sponsor before data transfer.

Ethics statement

The trial was approved by the London – South East Research Ethics Committee (REC reference: 22/LO/0015) on 25 February 2022.

Information governance statement

The University of Sheffield is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Sheffield is the Data Processor and Sheffield Teaching Hospitals is the Data Controller. We process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for Sheffield Teaching Hospitals Data Protection Officer, here: www.sth.nhs.uk/about-us/general-data-protection-regulations.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJMM1724.

Primary conflicts of interest: Ying Cheong has received Speakers' fees from Ferring, Merck, Abbott and Nordic Pharma and is a minor shareholder at Complete Fertility.

Andrew Drakeley has received payment for speaking at Ferring, occasional medical reports, support for attending Ferring and IBSA, and consulting fees for TMRW life science and Cambridge clinical laboratories.

Raj Mathur has received payment for medicolegal expert opinion for cases in their field of expertise.

We endeavour to obtain ICMJE disclosure of interests forms for all named authors. In this case, we have been unable to obtain these forms for every author. Please contact the corresponding author if you have any queries.

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as ISRCTN71978064.

Publications

Lumley E, O'Cathain A, Drabble S, Pye C, Brian K, Metwally M. Managing ovarian hyperstimulation syndrome: a qualitative interview study with women and healthcare professionals. *J Clin Med* 2023;**32**:6599–610. https://doi.org/10.1111/jocn.16701

Pye C, Tinkler L, Metwally M. Clinical research nurse and midwife as an integral member of the Trial Management Group (TMG): much more than a resource to manage and recruit patients. *BMJ Lead* 2023;**7**. https://doi.org/10.1136/leader-2022-000641

Lumley E, O'Cathain A, Ridsdale K, Drabble S, White D, Pye C, *et al*. Views on outpatient paracentesis and GnRH antagonists for ovarian hyperstimulation syndrome: a qualitative study of patients and healthcare professionals [published online ahead of print February 25 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJMM2923

The following was still under review when this synopsis was published. The following preprint version is available for the reader; please be aware this may not have been peer reviewed:

Metwally M, Ridsdale K, Dimairo M, Pye C, Cheong Y, Desoya L, *et al*. Ovarian Hyperstimulation Syndrome: The STOP-OHSS RCT of outpatient paracentesis and survey on preventive practices. *medRxiv* 2025. https://doi.org/10.1101/2025.07.18.25331764

Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number NIHR128137.

This synopsis provided an overview of the research award *STOP-OHSS (Shaping and Trialling Outpatient Protocols for Ovarian HyperStimulation Syndrome): A randomised controlled trial to assess the clinical and cost-effectiveness of active outpatient management of Ovarian HyperStimulation Syndrome*. For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR128137).

About this synopsis

The contractual start date for this research was in December 2019. This synopsis began editorial review in February 2025 and was accepted for publication in August 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' synopsis and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this synopsis.

List of supplementary material

Report Supplementary Material 1
STOP-OHSS Consensus Development Panel documents

Supplementary material can be found on the NIHR Journals Library article page (https://doi.org/10.3310/GJMM1724).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

CTRU	Clinical Trials Research Unit
CUA	cost–utility analysis
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FBC	full blood count
GnRH	gonadotropin-releasing hormone
GP	general practitioner
hCG	human chorionic gonadotropin
HCP	healthcare professional
ICSI	intracytoplasmic sperm injection

ISRCTN	International Standard Randomised Controlled Trial Number
IVF	in vitro fertilisation
OHSS	ovarian hyperstimulation syndrome
OP	outpatient paracentesis
PIS	participant information sheets
PPI	patient and public involvement
RCT	randomised controlled trial
R&D	research and development
REDCap	Research Electronic Data Capture
SAP	statistical analysis plan
SOP	standard operating procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	usual care

References

1. Royal College of Obstetricians and Gynaecologists. *RCOG Green-top Guideline No. 5: The Management of Ovarian Hyperstimulation Syndrome*. London; 2016.
2. Boothroyd C, Karia S, Andreadis N, Rombauts L, Johnson N, Chapman M; Australasian CREI Consensus Expert Panelon Trial evidence (ACCEPT) group. Consensus statement on prevention and detection of ovarian hyperstimulation syndrome. *Aust N Z J Obstet Gynaecol* 2015 [cited 9 December 2019];**55**:523–34. http://doi.wiley.com/10.1111/ajo.12406
3. NHS Digital. *Hospital Episode Statistics, Admitted Patient Care - England, 2010–11*. 2011. URL: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/hospital-episode-statistics-admitted-patient-care-england-2010-11#resources (accessed 14 January 2020).
4. Smith LP, Hacker MR, Alper MM. Patients with severe ovarian hyperstimulation syndrome can be managed safely with aggressive outpatient transvaginal paracentesis. *Fertil Steril* 2009;**92**:1953–9.
5. Lincoln SR, Opsahl MS, Blauer KL, Black SH, Schulman JD. Aggressive outpatient treatment of Ovarian Hyperstimulation Syndrome with ascites using transvaginal culdocentesis and intravenous albumin minimizes hospitalization. *J Assist Reprod Genet* 2002;**19**:159–63.
6. Gustofson RL, Browne P, Van Nest RL, Richter KS, Larsen FW. Aggressive outpatient management of severe ovarian hyperstimulation syndrome avoids complications and prolonged disease course. *Fertil Steril* 2005;**84**:S95.
7. Fluker MR, Copeland JE, Yuzpe AA. An ounce of prevention: outpatient management of the ovarian hyperstimulation syndrome. *Fertil Steril* 2000;**73**:821–4.
8. Shrivastav P, Nadkarni P, Craft I. Day care management of severe ovarian hyperstimulation syndrome avoids hospitalization and morbidity. *Hum Reprod* 1994 [cited 9 December 2019];**9**:812–4. URL: https://academic.oup.com/humrep/article/635454/Day
9. Abuzeid MI, Nassar Z, Massaad Z, Weiss M, Ashraf M, Fakih M. Pigtail catheter for the treatment of ascites associated with ovarian hyperstimulation syndrome. *Hum Reprod* 2003 [cited 15 January 2021];**18**:370–3. URL: https://academic.oup.com/humrep/article/18/2/370/639217
10. Abuzeid M, Warda H, Joseph S, Corrado MG, Abuzeid Y, Ashraf M, Rizk B. Outpatient management of severe ovarian hyperstimulation syndrome (OHSS) with placement of pigtail catheter. *Facts Views Vis ObGyn* 2014;**6**:31–7.
11. Lainas GT, Kolibianakis EM, Sfontouris IA, Zorzovilis IZ, Petsas GK, Tarlatzi TB, *et al*. Outpatient management of severe early OHSS by administration of GnRH antagonist in the luteal phase: an observational cohort study. *Reprod Biol Endocrinol* 2012 [cited 9 December 2019];**10**:69. URL: http://rbej.biomedcentral.com/articles/10.1186/1477-7827-10-69
12. Chappell N, Gibbons WE. The use of gonadotropin-releasing hormone antagonist post-ovulation trigger in ovarian hyperstimulation syndrome. *Clin Exp Reprod Med* 2017;**44**:57–62.
13. Bonilla-Musoles FM, Raga F, Castillo JC, Sanz M, Dolz M, Osborne N. High doses of GnRH antagonists are efficient in the management of severe ovarian hyperstimulation syndrome. *Clin Exp Obstet Gynecol* 2009 [cited 14 January 2020];**36**:78–81. URL: www.ncbi.nlm.nih.gov/pubmed/19688946
14. Lainas G, Kolibianakis E, Sfontouris I, Zorzovilis I, Petsas G, Lainas T, *et al*. Serum vascular endothelial growth factor levels following luteal gonadotrophin-releasing hormone antagonist administration in women with severe early ovarian hyperstimulation syndrome. *BJOG* 2014 [cited 9 December 2019];**121**:848–55. http://doi.wiley.com/10.1111/1471-0528.12572
15. Lainas GT, Kolibianakis EM, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas TG, Tarlatzis BC. Pregnancy and neonatal outcomes following luteal GnRH antagonist administration in patients with severe early OHSS. *Hum Reprod* 2013 [cited 9 December

2019];**28**:1929–42. URL: https://academic.oup.com/humrep/article-lookup/doi/10.1093/humrep/det114

16. Hosseini MA, Mahdavi A, Aleyasin A, Safdarian L, Bahmaee F. Treatment of ovarian hyperstimulation syndrome using gonadotropin releasing hormone antagonist: a pilot study. *Gynecol Endocrinol* 2012;**28**:853–5.
17. Lumley E, O'Cathain A, Drabble S, Pye C, Brian K, Metwally M. Managing ovarian hyperstimulation syndrome: a qualitative interview study with women and healthcare professionals. *J Clin Nurs* 2023;**32**:6599–610.
18. Lumley E, O'Cathain A, Ridsdale K, Drabble S, White D, Pye C, *et al*. Views on outpatient paracentesis and GnRH antagonists for ovarian hyperstimulation syndrome: a qualitative study of patients and healthcare professionals. *Health Technol Assess* 2026. https://doi.org/10.3310/GJMM2923
19. Waggoner J, Carline JD, Durning SJ. Is there a consensus on consensus methodology? Descriptions and recommendations for future consensus research. *Acad Med* 2016;**91**:663–8. https://doi.org/10.1097/ACM.0000000000001092
20. White DA, Pye C, Ridsdale K, Dimairo M, Mooney C, Wright J, *et al*. Outpatient paracentesis for the management of ovarian hyperstimulation syndrome: study protocol for the STOP-OHSS randomised controlled trial. *BMJ Open* 2024;**14**:e076434–11.
21. Metwally M, Ridsdale K, Dimairo M, Pye C, Cheong Y, Desoysa L, *et al*. Ovarian Hyperstimulation Syndrome: the STOP-OHSS RCT of outpatient paracentesis and survey on preventive practices. *MedRxiv* 2025. https://doi.org/10.1101/2025.07.18.25331764
22. Metwally, M. A trial evaluating active outpatient management to prevent hospital admission in women having fertility treatment who develop ovarian hyperstimulation syndrome. *ISRCTN* 2022. https://doi.org/10.1186/ISRCTN71978064
23. Dimairo M, Sutton L, Young T, Lee E, Mooney C, White D. STOP-OHSS Trial Simulation Report: summary report on sample size calculation and operating characteristics of the group sequential trial. *BMJ Open* 2024 (supplemental material). https://doi.org/10.1136/bmjopen-2023-076434.
24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;**42**:377–81.
25. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. *Eval Program Plann* 1979;**2**:197–207.
26. State of the fertility sector 2022/23 | HFEA. URL: www.hfea.gov.uk/about-us/publications/research-and-data/state-of-the-fertility-sector-2022-2023/
27. HFEA. Ethnic diversity in fertility treatment 2018. URL: www.hfea.gov.uk/about-us/publications/research-and-data/ethnic-diversity-in-fertility-treatment-2018/
28. Luke B, Brown MB, Morbeck DE, Hudson SB, Coddington CC, Stern JE. Factors associated with ovarian hyperstimulation syndrome (OHSS) and its effect on assisted reproductive technology (ART) treatment and outcome. *Fertil Steril* 2010;**94**:1399–404.
29. Abbara A, Patel B, Parekh I, Garg A, Jayasena CN, Comninos AN, Dhillo WS. Ovarian Hyperstimulation Syndrome (OHSS) requiring Intensive Care Unit (ICU) admission between 1996–2020 in England, Wales, and Northern Ireland. *Front Endocrinol (Lausanne)* 2022;**13**:1060173.
30. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, *et al*. *Unit Costs of Health and Social Care 2023 Manual. Technical Report*. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York), Kent, UK; 2024. https://doi.org/10.22024/UniKent/01.02.105685
31. *National Cost Collection 2021/22*. URL: www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ (accessed 10 July 2024).

Appendix 1 Results of the retrospective review and subsequent amendments to the randomised controlled trial design

A total of seven responses were received from sites. Six of these were returned before, and presented at, the TSC meeting. Only five of these contained data on mild/moderate OHSS cases; one response was excluded from analysis. All included responses are presented in *Table 3*.

The TSC agreed with the central team to remove the GnRH arm in the original design (demonstrated in *Figures 3* and *4*). The final retrospective review response received after the TSC meeting did not considerably affect incidence or hospitalisation rates or affect this decision.

TABLE 3 Results of the retrospective review

	Early OHSS	Late OHSS	Combined
Grant application estimates			
Estimated cases per site per year	11	4	15
Estimated randomised at 40% consent rate, per site per year	4.5	1.5	6
Estimated OHSS-related hospitalisation rates	Control 30%, intervention 10%	Control approximately 50%	N/A
Interim retrospective review data (five sites)			
Mean estimated cases per site per year	5	7.4	12.4
Estimated randomised at 40% consent rate	2	3	5
Estimated OHSS-related hospitalisation rates	48%	38%	42%
Final retrospective review data (seven sites)			
Mean estimated cases per site per year	4.6	6.5	11.1
Estimated randomised at 40% consent rate	1.8	2.6	4.4
Estimated OHSS-related hospitalisation rates	50%	41%	40%

N/A, not applicable.

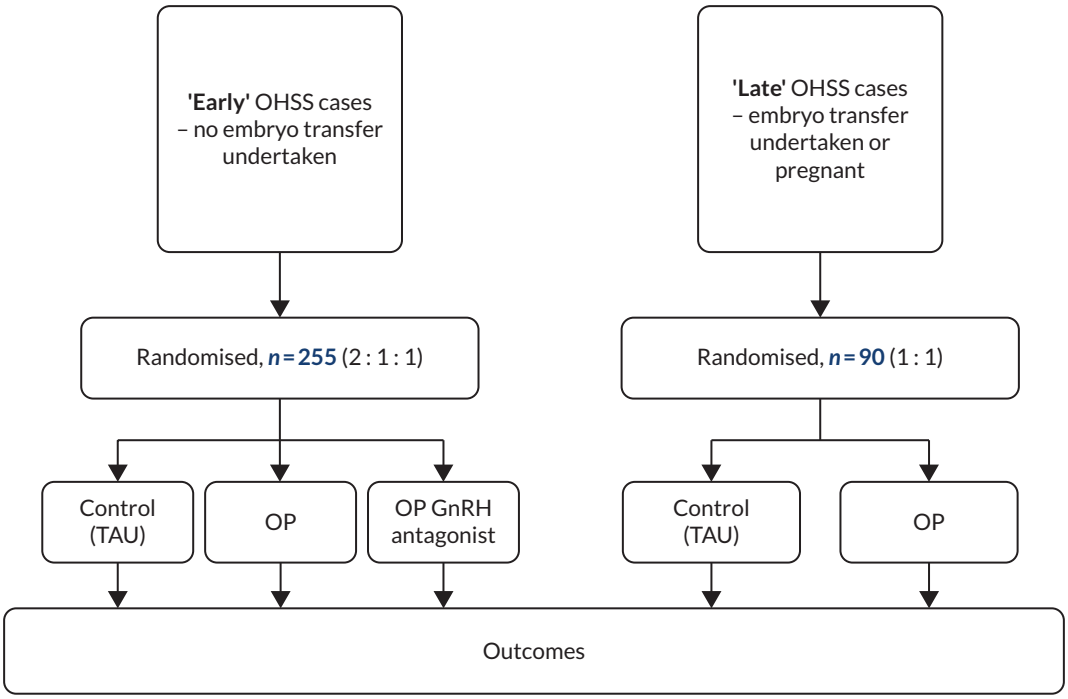

FIGURE 3 Original RCT design. TAU, treatment as usual.

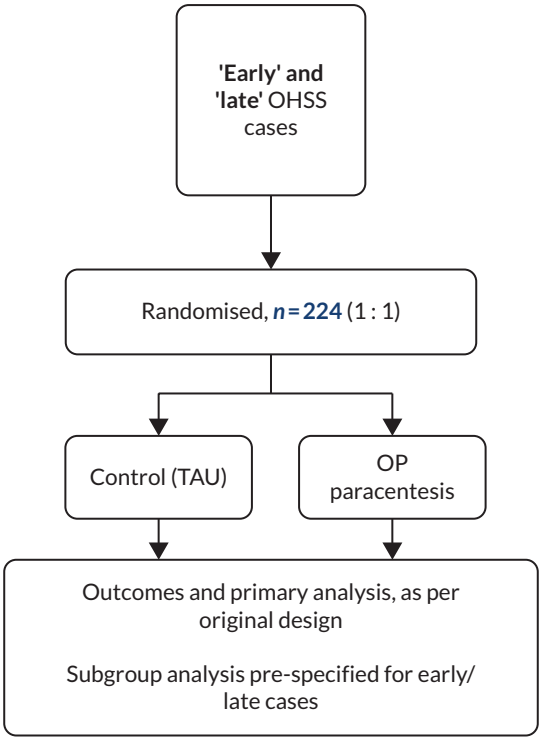

FIGURE 4 Amended RCT design. TAU, treatment as usual.

Appendix 2 Post-trial survey questions

Intro

STOP-OHSS substudy – Fertility Centre Survey
Further information can be found in the protocol, here: https://sites.google.com/sheffield.ac.uk/stopohss-trial/fertility-centre-survey

Aims

To examine if and how clinical practice at UK fertility units changed to reduce OHSS-related hospitalisations during and after the COVID-19 pandemic.

To provide insight into the consistency of approaches nationally and help inform future approaches.

Information

- We really appreciate the time you are taking to complete this survey. **Please answer all questions if possible.** If you are unable to answer a question, please tick or write 'Unknown'. You can leave the survey and return to it if u need to look into the data or enquire with others (note that this option will expire 1 month after starting the survey – at this point any responses you have already entered will be saved).
- We will request the name of your fertility centre, and an e-mail to contact with any queries. However, your site/centre identity will be anonymised in any dissemination of the survey findings.
- All fertility centres that complete the survey will be entered into a random **prize draw** for food delivery vouchers for the local team.
- Throughout the survey we refer to before/during/after COVID-19. Please use your own judgement for when you felt the impact of COVID-19 at your fertility centre. The WHO declared the outbreak as a Public Health Emergency of International Concern (PHEIC) on 30 January 2020, then no longer a PHEIC on 5 May 2023.

Do you routinely undertake planned (practice) 'Freeze all' cycles (not including fertility preservation for medical reasons)?

- ○ Yes
- ○ No
- ○ Unknown

Please provide details

Has your elective freeze rate for prevention of OHSS changed during/after COVID?

- ○ Yes
- ○ No
- ○ Unknown

If possible, please give approximate freeze rates

Before COVID

During COVID

After COVID

What is your thaw success rate of embryos?

At the blastocyst stage

At the cleavage/pronucleate stage

Is your clinical pregnancy rate (per egg transfer) from frozen embryos the same as it is for fresh embryos?

- ○ Yes
- ○ No
- ○ Unknown

Did the E-Freeze study influence your practice of freezing?

- ◯ Yes, it increased our elective freeze rate.
- ◯ Yes, it decreased our elective freeze rate.
- ◯ No, it did not influence our practice of freezing.
- ◯ Unknown

Do you routinely reduce the dose of stimulating hormones (drugs) during monitoring if you find an excessive ovarian response?

- ◯ Yes
- ◯ No
- ◯ Unknown

Do you use an antagonist protocol?

- ◯ Yes
- ◯ No
- ◯ Unknown

Did your practice of this change during COVID?

- ◯ Yes, our use of antagonist protocols increased during COVID.
- ◯ Yes, our use of antagonist protocols decreased during COVID.
- ◯ No, our practice stayed the same.
- ◯ Unknown

Has this change been maintained after COVID?

- ◯ Yes
- ◯ No
- ◯ Unknown

8. Do you use Cabergoline for prevention of OHSS?

- ◯ Yes
- ◯ No
- ◯ Unknown

Did your practice of this change during COVID?

- ○ Yes, our use of Cabergoline increased during COVID.
- ○ Yes, our use of Cabergoline decreased during COVID.
- ○ No, our practice stayed the same. Unknown

Has this change been maintained after COVID?

- ○ Yes
- ○ No
- ○ Unknown

9. Do you use GnRH trigger rather than hCG in women at risk of OHSS?

- ○ Yes
- ○ No
- ○ Unknown

Did your practice of this change during COVID?

- ○ Yes, our use of GnRH triggers increased during COVID.
- ○ Yes, our use of GnRH triggers decreased during COVID.
- ○ No, our use of GnRH triggers did not change during COVID. Unknown

Has this change been maintained after COVID?

- ○ Yes
- ○ No
- ○ Unknown

Did you change the dose of FSH in your standard protocols during COVID?

- ○ Yes, our dose of FSH in our standard protocols increased during COVID.
- ○ Yes, our dose of FSH in our standard protocols decreased during COVID.
- ○ No, our dose of FSH in our standard protocols did not change during COVID. Unknown

Has this change in practice been maintained since COVID?

- ○ Yes
- ○ No
- ○ Unknown

Did your single embryo transfer rate change during COVID?

- ○ Yes, our single embryo transfer rate increased during COVID.
- ○ Yes, our single embryo transfer rate decreased during COVID.
- ○ No, our single embryo transfer rate did not change during COVID. Unknown

Has this change in practice been maintained since COVID?

- ○ Yes
- ○ No
- ○ Unknown

Does your unit carry out paracentesis in the outpatient setting?

- ○ Yes
- ○ No
- ○ Unknown

Is this a practice you are considering in the future?

- ○ Yes
- ○ No
- ○ Unknown

Has there been any other change in how you manage women with symptoms of OHSS since the pandemic?

Do you believe the incidence of moderate and severe OHSS at your practice has changed during/after COVID?

- ○ Yes, I believe it decreased during/after COVID.
- ○ Yes, I believe it increased during/after COVID.
- ○ No, I believe it did not change during/after COVID. Unknown

Do you have any other comments on this topic?

What is the name of your Fertility Centre?

This information is only requested to ensure we only receive one response per site. Your site/centre identity will be anonymised in any dissemination of the survey findings.

Thank you for completing this survey. If you would like to be entered into the prize draw for the chance to win a £50 food delivery voucher for your centre (5 available!), please leave your email address.

Please only click 'next' if you have completed the survey. If you need to look into the data or enquire with others, you can leave the survey and it will save your answers for you to return to. This option will expire 1 month after starting the survey - at this point any responses you have already entered will be saved.

Powered by Qualtrics

Appendix 3 Overview of standard operating procedure review

TABLE 4 Summary of SOPs received from sites, categorised into codes

Codes		Summary
OHSS Definitions	Generic	Eleven sites describe OHSS as a complication of ovarian stimulation that women experience while undergoing fertility treatments, particularly when using treatment drugs such as Gonadotropins (hMG, FSH, hCG). Nine sites state that OHSS is characterised by ovarian enlargement, and the accumulation of fluid in the third space. Six sites suggest that patients will experience nausea and six sites said they will experience abdominal pain. Three sites also said that abdominal bloating will occur. Ten sites describe the condition as potentially life-threatening
	Early	Ten sites stated that early OHSS presents itself within 10 days of hCG administration, however the specifics are varied. Two sites defined early OHSS as presenting up to 10 days after hCG administration, two other sites suggested it presents within 9 days of hCG administration, and two sites suggested it was within 7 days of hCG administration. Two sites used egg collection as the marker, with one site stating early OHSS presents within 2–3 days of egg collection, and one site suggesting it was within 3–7 days of egg collection. One site states that early OHSS can be predicted by the number of oocytes retrieved and E2 concentrations at the time of hCG injection
	Late	Six sites state that late OHSS presents at around 10 days after a hCG injection, while 1 site said this presents between 12 and 17 days after the injection Nine sites associate late OHSS with achieving pregnancy, however one site emphasised that pregnancy should not be assumed, and sensitivity must be used when discussing this with patients. Six sites claim that late OHSS is more likely to progress to a severe condition and last longer than early OHSS
	Mild	One site states that mild OHSS occurs in 15% of all women undergoing IVF treatments, while one site stated that this is observed in up to 33% of assisted conception patients. Another site said it occurs in around one third of all IVF cycles Eight sites describe the main symptoms of mild OHSS as being abdominal bloating and mild abdominal pain, while seven sites also cite ovarian size of < 8 cm, and two sites claim that nausea is a possibility One site stated that patients experience gradual improvement as hCG levels drop, and in most cases completely resolve by the next menstrual period
	Moderate	Two sites state that moderate or severe OHSS occurs in 3–8% of women who undergo IVF treatment, and one other site specified the incidence rate as 7% Eight sites describe the main symptoms of moderate OHSS as being moderate abdominal pain and nausea/vomiting, while seven sites also listed symptoms of ovarian size 8–12 cm, and evidence of ascites (four of these sites require ultrasound evidence of ascites). Two sites listed symptoms of respiratory problems on minimum exertion and abdominal distension. Other symptoms listed by one site each included hypoproteinaemia, haematocrit 35–45%, progressive oliguria, diarrhoea, inability to maintain fluid intake, rapid weight gain and being unable to lie flat One site emphasised that moderate OHSS can progress to severe if pregnancy occurs, particularly where there is a multiple pregnancy due to higher levels of hCG
	Severe	Two sites state that moderate or severe OHSS occur in 3–8% of women who undergo IVF treatment, while two sites said the prevalence of severe OHSS is between 0.5% and 2%. One site specified that if more than 30 eggs are collected, the risk of severe OHSS is around 23%, and if the oestradiol level on the day of the hCG injection is > 20,000 pmol/l the risk is 38%. One site describe severe OHSS as potentially lethal Seven sites describe the main symptoms of severe OHSS as being clinical ascites (occasional hydrothorax), oliguria, haemoconcentration haematocrit > 45% and ovarian size usually of > 12 cm. Six sites stated hypoproteinaemia (serum albumin < 35 g/l) as a symptom, and three sites also listed hyponatraemia (sodium < 135 mmol/l), hypo-osmolality (osmolality < 282 mOsm/kg) and hyperkalaemia (potassium > 5 mmol/l) as symptoms. Two sites also noted other symptoms as shortness of breath, and a White blood cell count > 20,000/ml (one specifying > 25,000/ml), thromboembolic episodes and disordered hepatic function, while one site stated severe pain, dizziness and faintness, electrolyte imbalance and dehydration were symptoms

TABLE 4 Summary of SOPs received form sites, categorised into codes (*continued*)

Codes		Summary
	Critical	Eight sites describe the main symptoms of critical OHSS as oligo/anuria, while seven sites also listed haematocrit > 55%, thrombo-embolism and acute respiratory distress syndrome (ARDS). Six sites listed tense ascites or large hydrothorax, and five sites included a White blood cell count of > 25,000/ml. Two sites stated shortness of breath as a symptom, and one site listed further symptoms as severe pain, dizziness/faintness, dehydration and generalised oedema
Identification/ monitoring at risk patients		Eleven sites describe how to identify patients at a high risk of developing OHSS. The most frequently reported signs that a patient is at risk of OHSS are: PCOS, younger women (two sites specified: < 30/< 35), lower BMI (two sites specified < 20, < 25), high antral follicle count (four sites: > 16, > 18, > 20 × 2), high oestradiol levels, use of hCG as luteal support, pregnancy, previous OHSS, high anti-Müllerian hormone (5 sites: 20–30, > 25 × 2, > 35, > 50 pmol/l), high number of eggs collected (four sites: > 20 × 3, > 30) Five sites state that women considered at risk of developing OHSS with be appropriately counselled (given information and contact details if symptoms appear). One site specifies that all women with > 20 eggs after hCG trigger will be contacted by a doctor to enquire about OHSS symptoms. Another states that all patients receiving gonadotrophins as part of their fertility treatment will receive information about OHSS and what to do if symptoms appear
Diagnosis of OHSS	Screening tests	All sites provide symptoms indicative of OHSS to look out for. Four sites advise detail of the initial clinical examinations (include measurements for abdominal circumference, body weight, heart rate, blood pressure, respiratory examination, checking for vulval/leg swelling, hydration). Ten sites detail the screening tests required to confirm OHSS in those with symptoms. These all require FBC and U + E blood tests, and almost all require LFTs and clotting studies. Seven sites recommend a pelvic ultrasound scan and four sites recommend serum osmolality. Other suggested screening tests include: CRP, ECG, E2, and hCG if either ≥ 8 days or ≥ 10 days post embryo transfer, arterial blood gas test, D-dimer, Chest X-ray, CTPA or V/Q scan
	Differential diagnoses	Three sites provide possible alternative diagnoses, which include: pelvic infection, pelvic abscess, appendicitis, ovarian torsion, bowel perforation, ectopic pregnancy, surgical causes, gastroenteritis, inter-abdominal haemorrhage. One additional site just states that other causes should be ruled out
Prevention	GnRH Antagonists	Three sites advise the continuation of a GnRH antagonist alongside cryopreservation of embryos if the risk of OHSS is deemed to be high. One site specifies this as > 20 follicles per ovary of > 12 mm in diameter
	Elective cryopreservation	Eleven sites advise that cryopreservation of all embryos should be discussed with patients showing signs of developing OHSS. Seven of these sites state specific parameters at which cryopreservation should be strongly considered. These parameters range between sites and include the following: • number of follicles (> 18, > 20, > 25, > 30, > 40) • size of follicles (> 10 mm, > 14 mm) • number of eggs collected (> 20, > 25, > 30) • oestradiol levels (14,000 pmol/l, 15,000 pmol/l, 20,000 pmol/l).
	Cabergoline	Six sites suggest considering the use of Cabergoline to prevent OHSS in at risk women, or those showing early symptoms, although one of these sites stated that there is low evidence that Cabergoline reduces the incidence of OHSS One site says it should be considered in women showing symptoms later in their cycle, and with a hCG trigger, and another more specifically defines when it is use should be considered (> 19 follicles > 11 mm, or > 20 eggs collected)
Outpatient management	Management advice	All 12 sites provided management advice in their SOPs with varying degrees of detail. Most sites state that they provide patients with counselling of what to do and who to contact if their symptoms worsen, including out-of-hours contact details. Ten sites provide more specific management advice, which includes the following: take oral analgesics, take antiemetics for sickness, ensure adequate hydration (including drinking to thirst, 2 l/day and 3 l/day), monitor urinary output. These sites also advise patients to contact them or their local A&E if they are worried that their symptoms are worsening, including the following: increase abdominal distension, reduced urinary output, weight gain, increased abdominal girth measurement, significant pain and shortness of breath

continued

TABLE 4 Summary of SOPs received form sites, categorised into codes (*continued*)

Codes		Summary	
	Paracentesis	Two sites stated that paracentesis may be used to treat patients with ascites as an outpatient. One of the sites states that this is part of their care for severe OHSS only. All other sites do not mention the use of paracentesis in an outpatient setting	
	GnRH antagonists	No sites suggest using GnRH antagonists to treat OHSS and two sites specifically state that there is currently insufficient evidence to support it is use	
	Monitoring	Regulatory	Only three sites specifically mention regulatory phone calls as a part of outpatient monitoring. Two sites state that patients should expect daily phone calls with a face-to-face review every 2–3 days and one site mentions 'telephone counselling' but does not provide details on the frequency
		Clinic visits	Four sites mention face to face visits in their monitoring procedures. Two of these say that a face to face review should be conducted every 2–3 days, with one also stating this review should be conducted earlier if symptoms appear to be worsening.
			One site states reviews should be conducted twice a week until complete resolution of symptoms and another says that face to face reviews should be scheduled depending based on individual needs of the patient, which include the following: symptoms, blood test results and patient anxiety
		Patient diary	No sites ask patients to complete a symptom diary as part of their outpatient monitoring procedure
		Measurements	Two sites provide details of the type and frequency of measurements that patient's should undertake as part of at home monitoring. Both sites state that weight measurements should be taken daily, and one of these sites also advises daily abdominal girth measurements, as well as monitoring fluid intake and urinary output
	Other		Five sites described other outpatient management treatments including thromboprophylaxis, preventing or correcting haemodynamic instability, anti-emetics and pain killers
			Two sites specified that patients with severe OHSS managed as outpatients should always be treated with thromboprophylaxis and low molecular weight heparin (LMWH)
Criteria for admission			Eleven sites gave advice for when to admit patients. Only one site did not mention who to admit. Some sites provide basic advice such as the type of OHSS, whereas others were more specific. Five sites stated that patients with severe OHSS should be admitted, three specified critical OHSS, and two advised considering admission for moderate OHSS
			Eight sites recommended that patients should be admitted due to pain that cannot be controlled at home. Seven sites required admission when fluid management cannot be adequately carried out by the patient, for example due to nausea/vomiting. Other admission criteria not covered by the severity diagnosis included: unable to attend for regular outpatient follow-ups; worsening OHSS; respiratory symptoms; clinical decision/concern; or just unable to cope at home
Resolution of symptoms			None of the sites specifically defined symptom resolution, however, one site stated that women should be discharged from follow-up when she is no longer symptomatic with normal bloods, has mild symptoms and normal bloods or mild symptoms and mildly disordered bloods but they are resolving.

A&E, accident and emergency; BMI, body mass index; CRP, C-reactive protein; CTPA, computed tomography pulmonary angiogram; ECG, electrocardiogram; PCOS, polycystic ovary syndrome.

Appendix 4 Consensus panel results

STOP-OHSS study protocol

- A key issue from the PPI member's perspective was the need to be aware that women are likely to be anxious during this RCT. Therefore, it was necessary to be careful with any messaging or information regarding the RCT and OHSS management, ensuring clear and concise communication without adding extra or concerns.
- Clarification was needed on whether to exclude women who had already experienced OHSS; exclusion would result in loss of a number of potential participants. This point was taken back to the trial lead statistician and the TMG for further discussion. The decision was made to continue to exclude women previously randomised who later present with moderate or severe OHSS in subsequent fertility treatment cycles.
- COVID has altered the way patient visits are conducted and the RCTs would need to reflect this by considering the use of virtual visits to collect research data when women were not required to attend in person for tests.
- Clarification was needed about centres already undertaking OP to enable them to participate in this RCT. After further discussion following the consensus meeting, the decision was made to seek clarification from sites regarding willingness to stop performing OP as part of 'UC' as part of the Site Feasibility Assessment.
- Clarification was needed of the process for patient referrals from other centres and their eligibility to participate in the RCTs.
- One doctor expressed concerns about the low numbers of women with moderate to severe OHSS that are seen at their centre and the implications for recruitment.

Outpatient paracentesis treatment protocol

- Participants agreed that guidance about how to do paracentesis was likely to be needed but should not be prescriptive, leaving room for clinical judgement and HCP preference.
- One doctor expressed a preference for the GnRH antagonist arm because it is easier to implement than paracentesis, with less time commitment from centres. However, other participants were confident that because some centres are already doing OP, any concerns could be overcome by the team offering support to centres.

Administration of gonadotropin-releasing hormone antagonists treatment protocol

- This protocol was presented as a potential treatment because at this stage in the study we were considering dropping this arm of the RCT.
- Participants found the treatment protocol acceptable with a few minor amendments and a request to look at individual site prescribing and dispensing arrangements during site set up and explore with the regulatory body if medication packaging needs to be collected.

Criteria for hospitalisation of patients (as a secondary outcome)

- No issues were raised with the criteria for measuring the hospitalisation secondary outcome. Some doctors had left the meeting when this issue was discussed so it was taken to the next TMG for discussion with doctors on the team. The criteria were found to be acceptable.

Patient diary

- Participants raised multiple concerns about the content of the diary, to the extent that we agreed to develop another version and circulate it to participants at a later date for further comment. Issues included:
  - Being clear about what data was required for the RCTs rather than clinical care.
  - The necessity, and best ways, of measuring pain, shortness of breath, and fluid input/output.
  - Additions to the measurement of girth (where to measure and to mark the abdomen) and weight.
  - The need for the diary to focus on RCT-relevant data only, and to make it as short as possible so women complete it.

Following the consensus meeting, we took the patient diary to the Sheffield Teaching Hospitals NHS Foundation Trust 'Reproductive Health Research Public Advisory Panel'. They suggested changes to the question about shortness of breath, and the need for additional instructions on how to add up fluid input and output totals. These changes were made and further discussion took place at a TMG meeting. The new diary was then circulated to the consensus panel members for review.

Appendix 5 Health economics report

STOP-OHSS health economics

Introduction

An interim and a full CUAs (n = 224 in total) were planned.[20] Given the early closure of the trial with only eight participants randomised, a CUA could not be carried out. The following sections provide a descriptive analysis only of the health economics data that have been collected as part of the STOP-OHSS trial.

Population

Eight randomised participants were recruited from three centres. Three participants were allocated to the OP arm and five to the conservative management arm. One of the participants did not complete the health resource use or the outcomes questionnaires but is included in the following sections given the intention to treat basis for the originally planned analyses.

Outcomes

Mean EuroQol-5 Dimensions scores

EuroQol-5 Dimensions, five-level version were collected at baseline, thereafter daily and at day 28. One participant completed the EQ-5D-5L at all time points; three participants only at baseline; one participant at baseline and day 28; one participant completed EQ-5D-5L at baseline and for seven consecutive days after that and one participant completed the measure at baseline and for 16 days up (*Figure 5*). In all the latter cases, the EQ-5D-5L score at the final follow-up is higher than at baseline. Caution needs to be exercised in interpreting the mean EQ-5D scores (*Table 5*). They have been presented only to show very preliminary indication of health-related quality of life at baseline and follow-up.

Paracentesis procedure

Two patients from the intervention group underwent the OP procedure in the outpatient setting vaginally. The third patient in the intervention group underwent the paracentesis procedure abdominally in an inpatient setting. The ascites volume ranged from 40 to 200 ml. One patient from the UC group underwent the paracentesis procedure vaginally in an inpatient setting where 3000 ml of ascites were drained. All procedures were carried out by a trained doctor.

Participants were monitored regularly which also involved blood tests. The total number of blood tests amounted to 31 with 17 of these done by three patients in the intervention group.

The original intention was to microcost the procedure by recording the time taken by various health professionals and the equipment used. However, as data was not collected across the sites, costs from the National Cost Collection were used instead (see *Total costs*).

Health resource use

Data using the health resource use questionnaire were collected at day 28 only where patients were asked to report their resource use for the past month.

Summary of total resource use

Table 6 displays the general practitioner (GP) and community services, and Hospital services, used overall. In addition, one patient in the conservative management arm underwent the paracentesis procedure where 3000 ml of ascites were drained. This procedure took place in an inpatient setting. The patient required fluids intravenously.

Unit costs used

The unit costs for the various GP and community services were obtained from the latest Unit Costs of Health and Social Care 2023 Manual.[30] The remaining of the costs were obtained from the National Cost Collection 2021/22 (www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/).[31] The latter costs were adjusted for inflation so that all costs pertain to the year 2022–23. *Table 7* displays information on how the unit costs were calculated.

Medication

Five patients were prescribed OHSS medications. The medications were coded to the following categories: pain relief, anti-emetic, anti-coagulant, preventative thrombosis, lower oestrogen and fluids. All costs were obtained from the *British National Formulary* online. For the five patients, the costs of OHSS medications ranged from £5.18 to £110. 31 (*Table 8*).

Patient cost questionnaire

The purpose of the patient cost questionnaire was to collect detailed and accurate information on the costs incurred by patients regarding their last clinical visit for their OHSS. The data were meant to feed into the societal analysis. Only three patients completed the patient cost questionnaire and they all travelled to their hospital appointment by car (*Table 9*). A cost of 45 pence per mile was used based on a government source (www.gov.uk/expenses-and-benefits-business-travel-mileage/

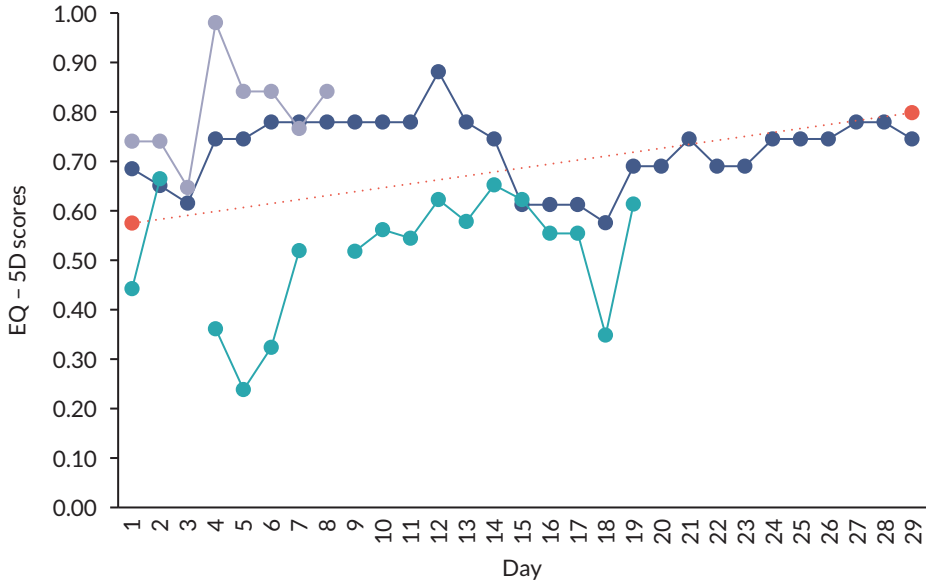

FIGURE 5 EuroQol-5 Dimensions, five-level version scores per patient.

TABLE 5 Mean EQ-5D-5L scores at the different time points

	OP		Conservative management	
	n	EQ-5D score (mean, SD)	*N*	EQ-5D score (mean, SD)
Baseline	3	0.622 (0.158)	4	0.488 (0.201)
Day 1	3	0.685 (0.048)		
Day 2	2	0.631 (0.022)		
Day 3	3	0.696 (0.312)		
Day 4	3	0.608 (0.324)		
Day 5	3	0.648 (0.283)		
Day 6	3	0.688 (0.147)		
Day 7	2	0.81 (0.044)		
Day 8	2	0.649 (0.185)		
Day 9	2	0.67 (0.154)		
Day 10	2	0.662 (0.166)		
Day 11	2	0.752 (0.183)		
Day 12	2	0.679 (0.142)		
Day 13	2	0.699 (0.066)		
Day 14	2	0.617 (0.007)		
Day 15	2	0.583 (0.041)		
Day 16	2	0.583 (0.041)		
Day 17	2	0.462 (0.161)		
Day 18	2	0.652 (0.054)		
Day 19	1	0.69		

continued

TABLE 5 Mean EQ-5D-5L scores at the different time points (*continued*)

	OP		Conservative management	
	n	EQ-5D score (mean, SD)	*N*	EQ-5D score (mean, SD)
Day 20	1	0.745		
Day 21	1	0.69		
Day 22	1	0.69		
Day 23	1	0.745		
Day 24	1	0.745		
Day 25	1	0.745		
Day 26	1	0.779		
Day 27	1	0.779		
Day 28	1	0.745	1	0.798

TABLE 6 Resource use – frequency of use

GP and community services	
GP	Two patients attended GP practice – one patient had four contacts at home and the other patients had one contact by phone
Midwife	One patient had two contacts with the midwife at the clinic and one patient had one contact with the midwife at the surgery.
Occupational therapist	One patient had two contacts with an NHS occupational therapist by phone
Hospital services	
Other NHS services	Two patients attended a planned visit to the early pregnancy unit for a 6-week scan
Hospital visits	The same patients who attended the early pregnancy visit also had two unplanned visits due to hyperemesis (excessive nausea and vomiting)

TABLE 7 Unit costs

Item	Unit cost (£)	Source	Notes
GP consultation – practice	56.00	Unit Costs of Health and Social Care 2023 Manual	Taken costs including direct care staff costs with qualification costs for a 10-minute appointment
GP consultation – home	56.00		Used the same as GP at practice as could not find a cost for home or cost per non-contact time
GP consultation – phone	43.92		Used average cost for an e consultation
Midwife – clinic	116.02		Used non-consultant led Midwifery service; Used the cost for a non-admitted Face-to-face follow-up appointment; currency code: WF01A; service code: 560
Midwife – surgery	53.00		Assume: similar costs to a practice nurse for 1-hour appointment given the patient population. Average time for a consultation is 20–30 minutes for uncomplicated pregnancy

TABLE 7 Unit costs (*continued*)

Item	Unit cost (£)	Source	Notes
NHS occupational therapist	109.44	National Cost Collection 2021/22[28]	Used non-consultant led occupational therapy Service; non-admitted face-to-face follow-up appointment; currency code: WF01A; service code: 651
6-week scan early pregnancy unit	64.90		Used average of all ultrasound scans
Outpatient visit – gynaecology	193.51		Used average of service code 502 – gynaecology service averaged over consultant-led and non-consultant-led for service code 502
Day case	641.08		Used average of all non-malignant gynaecological disorders
Blood tests	5.03		Used DAP08 – Phlebotomy
OP	478.18		Used antenatal other disorders NZ20A; did not use non-malignant gynaecology as there was no option with procedures
Inpatient paracentesis – small volume	1346		Used cost for a simple non-malignant gynaecological procedure – non-elective short stay (MB09A)
Inpatient paracentesis – large volume	1917		Used cost for a non-malignant gynaecological procedure – non-elective short stay (MB09C)

TABLE 8 Costs of OHSS medications per individual patients

Total OHSS medication costs per patient
£98.73
£110.31
£82.82
£13.95
£5.18

TABLE 9 Details about travelling to the last hospital appointment per individual patients

Time in minutes to travel			
To clinic	From clinic	Parking fee (£)	Total distance travelled in miles
40	40	5.00	25
30	30	2.50	–
20	30	7.00	4

rules-for-tax). Parking costs were directly collected from the patients.

Patients were also asked to report any loss in earnings in attending their last clinical appointment. They were also asked to report whether they were accompanied by someone to the appointment and if so, whether they incurred any loss in earnings (*Table 10*). Two patients reported that they were accompanied by someone, but their job type was missing. As a result, loss in earnings was only calculated for one patient. An hourly rate of £11.50 per hour was used for one of the patients who had a job in the catering industry.

Patients were asked how many days they were unable to do any of their usual activities and relied on someone else to help due to their OHSS in the last month. One patient reported 14 days, and one reported 15 days.

Total costs

Table 11 below shows the total costs incurrent by patients in the different groups. Only total costs are reported as the numbers are too low for averages to be meaningful (standard deviation are higher than means – not presented here). Significance between groups could not be assessed for the same reason of low numbers.

Conclusion

The sections above provide a descriptive analysis of the data collected for the planned health economics analysis. Out of the eight patients, seven only completed the outcomes data and the health resource use. Out of the seven, only three completed the patient cost questionnaire. Given the low numbers, means have not been calculated except for EQ-5D-5L. Unfortunately, conclusions cannot be drawn from the observations.

TABLE 10 Hours of loss in earnings for attending a clinical appointment

Loss in earnings		Hours of earnings lost	
Patient	**Person who accompanied patient**	**Patient**	**Person who accompanied patient**
Yes	Yes	6	8
No	–	0	–
Yes	Yes	4	4

TABLE 11 Total costs incurred by patients in the intervention and UC groups

	OP		Conservative management	
	Number of patients	**Total costs (£)**	**Number of patients**	**Total costs (£)**
Paracentesis procedures hospitalisation	3	2398	1	2052
Laboratory blood tests	3	86	5	70
Resource use				
GP visits	1	224	1	44
Midwifery services	1	232	1	53
NHS occupational therapist	0	0	1	109
Hospital services	1	2495	5	499
OHSS medication	2	124	3	187
Total costs – NHS and social care		5559		3014
Out of pocket costs[a]	1	234	2	53
Total costs – societal perspective		5793		3067

a This is based on only three people completing the patient cost questionnaire and only consists of travelling expenses and loss of earnings for one patient.