CONservative versus Standard carE for primary spontaneous PneumoThorax (CONSEPT)

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Glossary / abbreviations

AE	Adverse event
AMU	Acute medical admissions unit
AR	Adverse reaction
CI	Chief Investigator
BTC	Bristol Trials Centre
BTS	British Thoracic Society
CRF	Case report form
CTA	Clinical trial authorisation
CT-IMP	Clinical trial of an investigational medicinal product
CXR	Chest x-ray
DMSC	Data monitoring and safety committee
ED	Emergency Department
eDRIS	electronic Data Research and Innovation Service
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health technology assessment
GCP	Good clinical practice
ICD	Intercostal drain
ITT	Intention to treat
MACE	Major Adverse Cardiovascular Event
MHRA	Medicines and healthcare products regulatory agency
MI	Myocardial Infarction
NA	Needle aspiration
NBT	North Bristol NHS Trust
NIHR	National Institute for Health Research
NPSA	National Patient Safety Agency
ONS	Office for National Statistics
PCA	Patient controlled analgesia
PEDW	Patient Episode Database for Wales
PI	Principal Investigator
PIS	Patient information sheet
PSP	Primary spontaneous pneumothorax
RCT	Randomised controlled trial
REC	Research ethics committee
RSI	Reference safety information
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SpO2	Peripheral capillary oxygen saturation
SSA	Site Specific Assessment
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial management group
TSC	Trial steering committee
VAS	Visual analogue scale

1. Plain English Trial summary

Primary spontaneous pneumothorax (PSP) is an abnormal collection of air in the space between the lung and the chest wall, causing collapse of the lung. This type of pneumothorax is called primary, as it happens in patients with no underlying lung disease, and spontaneous, as it occurs without injury. Previous work by our group shows that 3,000 patients a year need admission to hospital to treat a PSP. Currently, patients with symptoms are treated by draining the air through a needle or tube put into the chest, as it is thought to reduce symptoms of pain and breathlessness and speed recovery. This treatment means patients often stay in hospital for one week and puts patients at risk of complications from treatment (for example, infection).

Patients whose lung has only partially collapsed (small PSP) or who have fewer symptoms can be managed “conservatively”, this means not draining the air, and being observed instead. However, it is not clear whether it is safe to do this in patients with symptoms and a larger collapse (large PSP). Research published in 2020 from Australasia compared draining the air with observation only in patients with large symptomatic PSP. The researchers found that observation was as good as draining the air but there were problems with the research and, although these results are promising, they have not changed how doctors treat patients.

The CONSEPT trial will investigate whether observation only in patients with a large symptomatic PSP is safe and effective with respect to outcomes that are important to patients, such as the need for invasive treatments and length of hospital stay.

Participants will be put into one of two groups by chance. The observation only group will not have the air drained but will be monitored for a few hours, and if comfortable and stable, discharged from hospital. The second group will be treated in the usual way by draining the air through a needle or tube. We will collect information to see if patients need to have a subsequent drainage in the first month after having the PSP, and measure symptoms and general health. We will also monitor whether the PSP recurs within a year.

2. Background

2.1 Spontaneous pneumothorax

Spontaneous pneumothorax has an incidence of 17-24 and 1-6 / 100,000 population / year for men and women, respectively[1]. When it occurs in patients without known underlying lung disease it is called Primary Spontaneous Pneumothorax (PSP)[1] . PSP patients are typically young with no medical comorbidities. There are 3,000 PSP admissions/year in the UK[2].

Contemporary UK guidance (British Thoracic Society [BTS] 2010) focuses on treating the acute presentation of PSP with short-term drainage (needle aspiration, (NA)), with a small bore cannula and manual aspiration[1]. The national guidelines in the United States advise using an intercostal drain (ICD) as first line treatment[3]. The drain is inserted through a small skin incision between the ribs and is typically sutured in place and attached to a large bottle containing water to form a seal, and left in place for at least 24 hours while the patient is admitted to hospital. Due to the increased length of hospitalisation with the intercostal drain, the BTS guidelines suggest this method of management only when initial needle aspiration fails, although it does allow for operator experience and patient choice in this decision,

acknowledging a higher risk of needing subsequent pleural procedure after needle aspiration than intercostal drain[1].

Ambulatory treatment involves insertion of a drainage device with an integral one-way valve (pleural vent), allowing patients to be discharged home with the device in situ. The effectiveness of the pleural vent has been demonstrated in a randomised controlled trial (RCT), undertaken by our group, which randomised 236 patients with PSP between pleural vent and standard care of NA±ICD, demonstrated shorter length of hospitalisation[4]. Ambulatory care with the pleural vent will form part of the suggested management of PSP in the next iteration of the BTS pneumothorax guidelines in 2023.

2.2 Evidence for use of conservative care in PSP

There is evidence that no intervention may be a valid strategy, with a recent Australasian trial comparing conservative care to ICD insertion in patients with large symptomatic PSP[5]. In this study, patients managed conservatively were observed for 4 hours, and if stable were discharged from hospital. The primary outcome for the study was radiological resolution of PSP on chest x-ray at 2 months and showed non-inferiority of conservative care and may reduce recurrence rate. Conservative care was safe with 15% of patients requiring a chest drain.

3. Rationale for the study

There were significant issues with the recent trial of conservative treatment, which has limited its adoption into routine clinical practice. The primary outcome was radiological appearance at 2 months, rather than a patient-focussed outcome. Only 10% of all eligible patients were enrolled, and participants were minimally symptomatic compared with our recent RCT of ambulatory PSP management[6]. Additionally, the control group (ICD) does not reflect standard care in the UK.

The optimal initial treatment remains contentious, and the results of the Australasian PSP trial have not changed NHS practice. This is likely due to a primary endpoint not felt to be important to physicians or patients in surveys conducted by this group; a comparator which does not reflect UK practice; and concern that participants do not reflect the population that are typically invasively managed in the UK[6]. We conducted a survey to understand current practice and equipoise, specifically to inform this application. Respondents comprised 85 UK physicians (74% emergency department (ED) doctors, 21% respiratory, 5% other). Responses demonstrated that, despite the recent trial [5], conservative care has not been widely adopted with none of the responders stating would they conservatively manage a patient with a large symptomatic PSP.

Ongoing invasive care potentially causes harm. A safety report from the National Patient Safety Agency (NPSA) reported 12 deaths and 15 cases of severe harm from chest drain insertion in England and Wales[7]. This is a voluntary reporting system, and it was felt that the true rates of harm to patients are likely to be substantially higher, given that healthcare staff are known to under-report incidents. Additionally, chest drains are inserted using guidewires, a skilled technique that can lead to patient harm if done incorrectly. A recent safety report highlighted that half the ‘Never Events’ in the Emergency Department over a two-year period were retained guidewires, where the guidewire was left in a body cavity[8].

4. Aims and objectives

Aim: To evaluate whether conservative care for large symptomatic PSPs is superior to usual care.

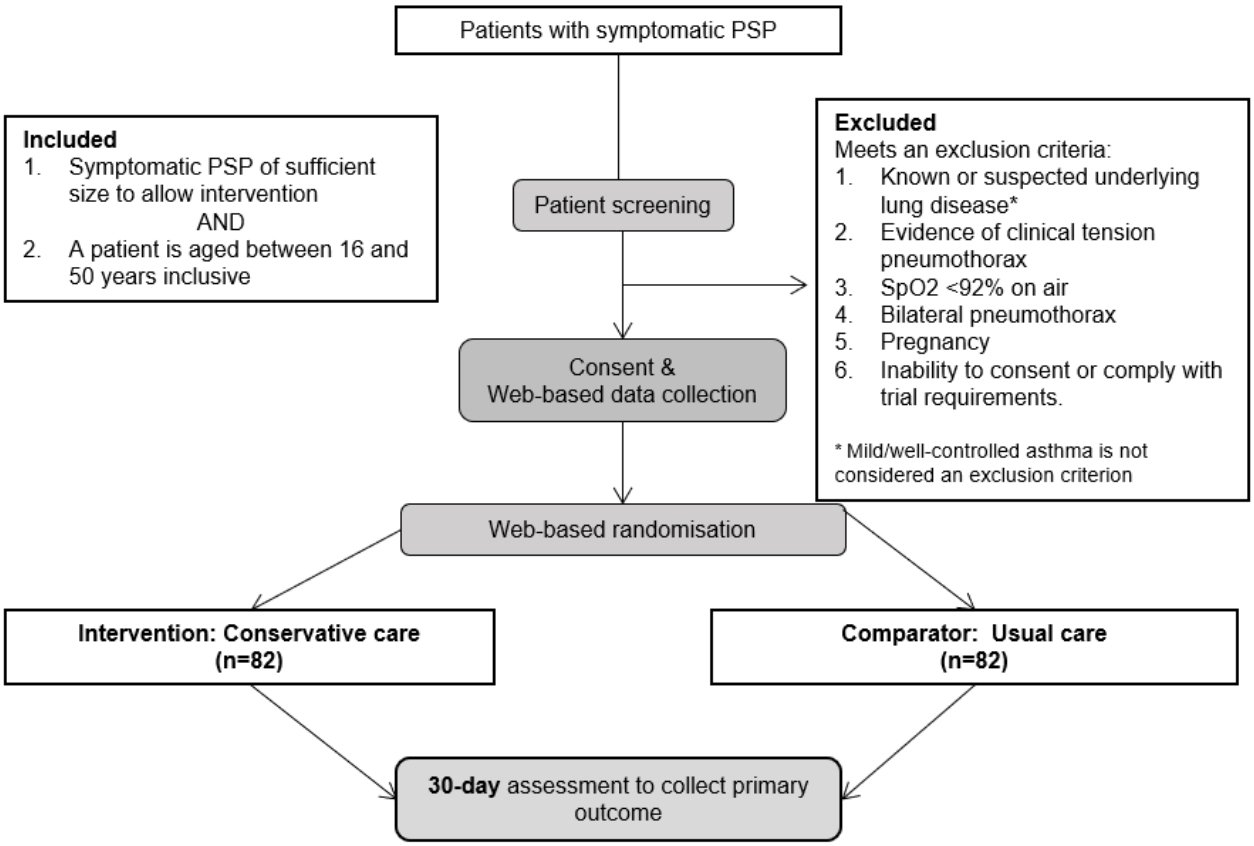
Objectives:

a) To estimate the difference between groups in the number of days spent in hospital, up to 30 days after randomisation, including initial hospital stay and re-admissions;

b) To test whether conservative care is superior to usual care with respect to subsequent pleural procedures over first 30 days.
c) To estimate the difference between groups with respect to a range of patient-reported and clinical secondary outcomes over first 30 days.
d) To estimate the difference in recurrence rates between groups over 12 months follow-up.
e) To estimate the cost-effectiveness of conservative care compared to usual care.

5. Plan of investigation

5.1 Trial schema



The sample size based on the original primary outcome was calculated as 638 participants (Conservative care n= 319 and Usual care n= 319). The trial schema has been updated to reflect the new primary outcome and sample size following the pilot review meeting outcome. See section 5.7.1 for further information.

5.2 Trial design

An open multicentre, parallel two-group, individually randomised RCT with an internal pilot phase, parallel cost effectiveness analysis and active participant follow-up to 30-days. The internal pilot will establish processes for, and test the feasibility of, recruitment. The full trial will test the hypothesis that conservative care compared to usual care reduces the number of days spent in hospital over the first 30 days.

5.3 Setting

At least 35 NHS hospitals secondary and tertiary level care NHS hospitals in England, Scotland and Wales, covering both urban and rural settings.

5.4 Key design features to minimise bias

Potential biases arising in a trial [9] will be avoided as follows:

Bias arising in the randomisation process:
This bias, due to systematic differences between baseline characteristics of the groups that are compared, will be ruled out by concealed randomisation (see Section 6.1)

Bias due to deviations from intended interventions:
This bias will only arise if co-interventions, not described as part of the assigned interventions, are administered differentially by group. This bias will also be minimised by defining procedures for participant follow-up and monitoring adherence to the protocol (see section on endpoint committee 5.7.1). Other deviations, e.g. non-adherence to the assigned intervention, will be described but will form part of the primary analysis by intention-to-treat (see Section 7.1).

Bias due to missing data:
This bias will be minimised by using established methods developed in the Bristol Trials Centre (BTC) to maximise the quality and completeness of the data, for example regular monitoring of data, detailed querying of data inbuilt into the study database, offering alternative methods for participating in follow-up (e.g. online or telephone if unable to attend in person). Instances of non-adherence will be documented and reviewed at study meetings and an action plan for maximising compliance drawn up as appropriate. Data will be analysed by intention to treat irrespective of future management and events and every effort will be made to include all randomised patients. The statistical analysis plan (SAP; see Section 7.1), finalised before locking the database and carrying out any comparative analyses, will describe the analytic strategy for managing missing data, which will be designed to minimise the risk of bias from this source. Prespecifying the strategy will minimise this bias.

Bias in the measurement of outcomes:
This bias arises when there are systematic differences between baseline groups in the measurement of outcomes, e.g. due to knowledge of assignment when making measurements. This trial cannot be blinded (see section 6.2) but includes features to minimise bias that may arise due to this limitation, including the use of an objective primary outcome measure and by

providing clear unambiguous definitions for each of the secondary outcome measures (see section 5.7).

Bias in selection of the reported result:
This bias arises when the reported result is chosen from multiple possible results in relation to its magnitude or statistical significance and without reporting other possible results. The prespecified SAP and Health Economics Analysis Plan will describe the analyses to be reported. Prespecifying these analyses will minimise this bias.

5.5 Trial population

The target population will be adults up to and including 50 years of age with symptomatic PSP of sufficient size and symptoms causing the treating physician to consider intervention.

5.5.1 Inclusion criteria

Patients will be eligible for the trial if ALL of the following apply:

1. Symptomatic PSP of sufficient size to allow intervention
2. Age between 16 and 50 years old (inclusive)

PSP is defined as a pneumothorax occurring in the absence of trauma and underlying lung disease. An upper age cut off of 50 years of age was selected, as patients above this age are more likely to have underlying lung disease as a cause for their pneumothorax (i.e. secondary and not primary pneumothorax).

5.5.2 Exclusion criteria

Participants may not enter study (i.e. may not be randomised) if ANY of the following apply:

1. Known or suspected underlying lung disease*
2. Evidence of clinical tension pneumothorax
3. SpO2 <92% on air
4. Bilateral pneumothorax
5. Pregnancy
6. Inability to consent or comply with trial requirements.

* *Mild/well-controlled asthma is not considered an exclusion criterion. Patients with a diagnosis of asthma who are well-controlled on standard prescribed inhaler therapy, remain eligible for participation in this study.

5.6 Trial interventions

5.6.1 Trial intervention: Conservative care

Participants randomised to conservative care should be managed *without* invasive intervention. They will observed for a period of around four hours from hospital presentation but the absolute observation period will be at the discretion of the treating clinician.

If during the observation period:

a) Patient wants intervention due to significant symptoms;
b) Patient develops physiological instability (SpO2 <92% on air, respiratory rate>25 breaths per minute);
c) Repeat chest radiograph demonstrating an enlarging pneumothorax with clinical concern from a senior clinician (e.g. ST4 or above) with the reason recorded.

They should undergo usual care (see section 5.6.2 below; procedure at the discretion of the treating physician). Reason(s) for providing usual care will be documented.

After the observation period the participant should be discharged if they meet all of the following criteria:

a) Symptoms controlled sufficiently to mobilise comfortably;
b) Acceptable vital signs to a senior physician;
c) No requirement for supplementary oxygen.

If any of the above criteria are not met, the patient will undergo usual care (below).

5.6.2 Comparator: Usual care

The comparator will reflect usual invasive care and comprise of either NA or ICD or pleural vent. The initial pleural procedure administered is at the discretion of the treating clinician.

Needle aspiration (NA)
NA should be attempted as per BTS guidelines and in accordance to local protocols. A routine post procedure chest radiograph should be performed.

Decisions regarding further intervention should be guided by degree of symptoms and physiological parameters. If asymptomatic and acceptable vital signs as judged by a senior physician (e.g. ST4 or above) , then the patient can be discharged with follow-up. If the patient remains symptomatic or physiologically unstable then the chest radiograph should be used to determine if an ICD is feasible and guide insertion site. If the patient is symptomatic and there is sufficient intrapleural distance (≥2cm) then a small-bore ICD (≤14F) should be inserted and attached to an underwater seal bottle. This would count as a subsequent pleural procedure (i.e. a primary outcome event).

Intercostal chest drain (ICD)
The ICD will be inserted as per BTS guidelines. This should be small (<14F) and should be connected to a drainage system (the underwater seal bottle or Heimlich valve). Decisions regarding ICD removal will follow BTS guidelines and standard practice at the participating centre. Clinicians may decide to proceed directly to ICD insertion and admission at their

discretion[1]. The reasons for not attempting initial needle aspiration in these cases will be recorded on the case report form (CRF).

Pleural vent
Although not yet part of the guidelines, expert opinion suggests that ambulatory management will be included in the updated guidelines (BTS 2023), and hence it will be an option for usual care in this trial to future-proof the study result for the anticipated change in guidelines.

If ambulatory management is selected as the primary treatment modality (dependent on facilities and established practices at sites) it should be inserted as per BTS guidelines for pleural procedures. Following device insertion, patients will be observed for 1–2 hours after which a chest radiograph should be repeated.

If the chest radiograph shows insufficient lung re-expansion (as defined above for Needle Aspiration), the ambulatory device should remain in situ and the patient be discharged if:

a) Symptoms are controlled sufficiently to mobilise comfortably;
b) Acceptable vital signs according to a senior clinician (heart and respiratory rate, blood pressure, oxygen saturations);
c) There is no requirement for supplementary oxygen.

If the chest radiograph shows sufficient re-expansion of the lung and no ongoing air leak, the device can be removed, and the patient discharged. As standard practice, a post-removal chest radiograph should be performed to ensure that the lung has not re-collapsed.

5.7 Primary and secondary outcomes

5.7.1 Primary outcome

Number of days in hospital up to 30 days after randomisation, including initial hospital stay and re-admissions

i) Pilot Phase

During the pilot phase (0 to 14 months), the stated primary outcome was: Any pleural procedure (including ICD insertion, Needle Aspiration, pleural vent, video-assisted thoracoscopy) administered at any time after randomisation and completion of initial care up to 30 days after randomisation. This primary outcome was chosen to reflect the patient survey's findings, which indicated that reducing the risk and number of invasive procedures was the top priority for patients. A 30-day endpoint was chosen as this was expected to capture the requirement for intervention due to failed initial care.

ii) Main Phase

A review meeting was held with the funder in September 2024 during which the progression criteria were reviewed (see section 6.7.1) Due to a lower than expected recruitment rate during the pilot period, it was clear that it would not be feasible to meet the overall target of 638 participants required to power the analysis of the original primary outcome. With this in mind, the outcomes were re-evaluated for clinical importance. Number of days in hospital up to 30

days after randomisation, including initial hospital stay and re-admissions, is considered clinically important in this patient population and has the potential to influence guidelines and alter current practice. If there is a significant safety or patient reported outcome signal, either positively or negatively towards conservative management, this would refine the current guidelines and provide clear indications of when conservative management should be used, either widening its use and thereby saving interventions, or limiting its use appropriately. The Trial Steering Committee chair and the trial Patient Advisory Group further support this as an important outcome and the funder approved the change in primary outcome.

The primary outcome of number of days in hospital will be captured on CRFs at discharge and at the 30 day follow up visit, based on comprehensive review of medical notes and discussion with the participant (face to face or by telephone).

5.7.2 Secondary outcomes

1. Any pleural procedure (including ICD insertion, Needle Aspiration, pleural vent, video-assisted thoracoscopy) administered at any time after randomisation and completion of initial care up to 30 days after randomisation.
2. Pain and breathlessness visual analogue scale (VAS) scores measured at baseline, 48 hours, 14 and 30 days collected using an online application.
3. Participant-reported health status (EQ-5D-5L questionnaire) measured at baseline, 48 hours, 14 and 30 days collected using an online application.
4. Perceived participant acceptability of the intervention or comparator at and 30 days collected using an online application
5. Radiographic resolution of PSP at 30 days
6. Adverse events up to 30 days
7. Total number of subsequent pleural procedures up to 30 days.
8. Time to return to work (if employed)
9. Hospital resource use up to 12 months, including emergency, admitted, critical and outpatient care
10. Time to recurrence of pneumothorax up to 12 months (estimated at 12 months).

Recurrence will be defined as either an ipsilateral PSP (on the same side as the PSP at time of recruitment) or contralateral PSP (on different side to the PSP at the time of recruitment) after the participant has met the definition of radiographic resolution of the PSP at day 30 (+/- 7 days).. Patients with incomplete pneumothorax resolution on chest radiograph at this point will be excluded from analysis of this outcome.

5.8 Sample size calculation

5.8.1 Sample size based on outcome defined in pilot phase

The sample size based on the primary outcome of need for further pleural procedures was set at 638 participants (319 per group) which provided 90% power to detect an absolute difference of 12% (34% relative risk reduction) between groups assuming a 35% event rate in the usual care group, that 5% of participants would be lost to follow-up and 1% would cross-over.

Outcome frequency in the comparator (usual care) group was based on data from the RAMPP study assuming initial treatment is either needle aspiration (NA), ICD or pleural vent. In the RAMPP study, approximately 75% of patients had Needle Aspiration as a first procedure with a

reintervention rate of 50%, and 25% had ICD as first procedure with a reintervention rate of 16.7%. The re-intervention rate for pleural vents in RAMPP was 24/114 (21%). It was anticipated from our clinician survey that 50% of clinicians would opt for Needle Aspiration as first line treatment, with 25% opting for pleural vent and 25% ICD, providing an overall estimated rate of subsequent pleural procedure of 35%. The attrition rate for the 30-day primary outcome in RAMPP was 4% (9/236)[4].

The reintervention rate in the Brown *et al* study, which compared interventional management against conservative management in patients with PSP, was 25/162 (15%) in an 8 week period[5] We anticipate that the rate of subsequent pleural procedures will be higher in CONSEPT due to differences between the study populations. For example, we expect the inclusion of patients with a previous history of a pneumothorax will increase the rate of early recurrence.

The proposed effect size in CONSEPT was based on what we judged to be the largest sample size that the study could realistically achieve within a duration that would not exhaust the motivation of sites and deliver an answer as quickly as possible, important both for the benefit of future patients and the NHS.

5.8.2 Updated sample size using outcome defined in main phase (length of hospital stay)

Using the new primary outcome of number of days in hospital (up to 30 days), we have set a revised sample size of 164 patients (82 per group) which will provide 90% power (at 5% 2-sided statistical significance) to detect a reduction of 1.5 days in the intervention arm assuming a median length of stay of 3.5 days in the control arm, that 2.5% of patients will be lost to follow-up and 5% will cross-over [15]. The amended rates of loss to follow-up and cross-over are guided by those seen in the first 40 randomised trial participants[10]. The anticipated median length of stay is based on the RAMPP study findings[4] of a median of 4 days in their control arm, reduced to allow for some patients in this arm being treated with a pleural vent in CONSEPT as per the updated BTS guidelines. The interquartile range for the length of stay in the control arm would be assumed to be the same as in the RAMPP paper (0-8 days) to provide a conservative estimate. The clinicians on the study team have informed these decisions and determined a reduction to days in hospital of 1.5 days to be of clinical relevance in practice. This sample size is achievable based on the observed recruitment rate between 1/1/2024 and 31/7/2024 of 0.21 patients per centre per month.

To achieve this sample size, we intend to recruit at least 35 sites and to use methods developed for other studies managed by the Bristol Trials Centre to maximise out-of-hours recruitment, e.g. trainee research networks.

6. Trial methods

6.1 Description of randomisation

Participants will be randomised 1:1 to either conservative care or usual care immediately after the PSP has been diagnosed in the Emergency Department (ED) or acute medical admissions unit (AMU). Randomisation will be carried out using a secure web-based internet-based

randomisation system ensuring allocation concealment. Cohort minimisation (with a random element incorporated) will be used to ensure balance across groups with respect to first/recurrent pneumothorax and the allocation will be stratified by centre. Cohort minimisation on first/recurrent pneumothorax will be used because this has been shown to influence the risk of recurrence, and may influence other study outcomes.

6.2 Blinding

This trial cannot be blinded because decisions may need to be taken 24/7 by a physician unconnected with the trial. The trial includes features to minimise bias that may arise due to this limitation (see Section 5.4).

6.3 Research procedures

6.3.1 Research assessments

Consent should be taken on paper. It will include consent for access to routine data including Hospital Episode Statistics, (HES), Patient Episode Database for Wales (PEDW), and electronic Data Research and Innovation Service (eDRIS). Baseline characteristics will be collected after consent and before randomisation on purpose-designed CRFs.

A research visit should be conducted at day 30 day (+7 days). At this visit, the patients will undergo a chest radiograph and complete the EQ-5D-5L questionnaire and record their pain and breathlessness using a VAS (see Section 6.5 for further details). Patients will also be asked to complete an online EQ-5D-5L questionnaire and record their pain and breathlessness using a VAS at 48hrs and day 14.

A minimum clinical follow-up (within 7-10 days time) is recommended for patients managed on the ambulatory or conservative pathway to ensure patient safety.

Follow-up beyond 30-days will be using HES, PEDW and eDRIS admitted, critical, emergency and outpatient data, to determine any further admissions and hospital contacts up to 12 months. This method of follow-up will avoid the need to follow participants prospectively, which can be challenging for this patient group who frequently do not attend.

6.4 Definition of end of trial

All participants will be actively followed up to the primary end point (30 days) and for at least another 5 months (up to 6 months) using routine data. Participants recruited in the last 3-4 months of the recruitment period will be censored early (at 6 rather than 12 months). The end of the trial as a whole will be after all trial participants have completed follow up, all data queries have been resolved, the database locked and the analysis completed.

6.5 Data collection

Data will be only collected that are directly related to the study research questions (see Table 2). Baseline characteristics, including smoking history (including cannabis), health status (EQ-5D-5L) and 100mm VAS for pain and breathlessness will be collected prior to randomisation on purpose-designed CRFs.

Outcome data will be collected at follow-up appointments and from routine data (see Section 6.3).. If the patient cannot attend the day 30 appointment face-to-face, they can be contacted over telephone or teleconferencing software. Sites will be required to review all hospital activity (in-patient and out-patient) for their participants, and to review notes in detail for any patient who is admitted. EQ-5D-5L will be completed online with email prompting, and URL for responses.

Table 2: Data collected from each participant for the trial duration.

Data collection	Pre-screening	Enrolment & randomisation	Discharge	Follow-up			
Time		0		Online 48 hrs (±24 hrs)	Online 14 days (±72 hrs)	30 days (+1 week)	Up to 12 months
Eligibility assessment	X	X					
Provide PIL	X						
Consent		X					
Chest radiograph	X					X	
Clinical assessment		X				X	
Length of hospitalisation		X	X			X	
Pleural interventions		X	X			X	
Surgical procedures			X			X	
Assessment of pain/ breathlessness (VAS)		X		X	X	X	
Hospital re-attendance						X	X
Resolution of PSP						X	
EQ-5D-5L score		X		X	X	X	
Acceptability questionnaire						X	
Routine data							X
Pneumothorax recurrence							X
Adverse events		Recorded as and when they occur up to 30 days post randomisation					

6.6 Source data

The primary data source will be the participant's medical notes, alongside the data collection forms for the study inputted on the online trial database. For 12-month follow-up the primary source data is the participants linked HES activity data.

6.7 Planned recruitment rate

Anonymised HES data and data from RAMPP (3) was used to inform the recruitment projections. Overall, there are ≈1700 eligible cases/year in England, treated in >140 hospitals, with 50% of cases treated in 30% of hospitals. An original target recruitment rate was set at 0.7 participants/centre/month (modelled from RAMPP). Higher recruitment rates than RAMPP were anticipated, making this projection cautious, as the CONSEPT trial intervention is conservative, rather than insertion of a new device requiring bespoke training.

The target recruitment rate was reduced to 0.21 participants/centre/month following the pilot study, with the target set based upon study recruitment between January and July 2024.

6.7.1 Pilot study: Progression criteria

The pilot will monitor 1) recruitment rates (proportion of screened patients eligible, eligible patients consented and randomised); 2) adherence to the allocated treatment; 3) rates of completion of the primary outcome. Strategies will be developed to tackle barriers by collecting and inspecting reasons for non-participation.
Criteria for progression from phase 1 to phase 2 are outlined in Table 1.
These targets allow for staggered site opening. If all criteria are green, we will proceed to a full trial with the same protocol; if one or more criteria are amber, we will propose adaptions to address the short fall; if one or more criteria are red, we will discuss with the trial steering committee and funder whether the full trial is feasible. The results from the internal pilot will be central to an Investigators' meeting to share best recruiting practices.
In the main phase, further sites will be opened (minimum 35 sites) recruiting the remaining 478 participants.

Table 1: Progression criteria (after 14 months of active recruitment)

Criterion	Target	Green	Amber	Red
Participant recruitment	160	≥160	128-159	<128
Centres open	24	24	20-23	<20
Randomisation rate/centre/month	0.7	≥0.7	0.5-0.69	<0.5
Adherence to allocated intervention	100%	100%	90-99%	<90%
Primary outcome data available	95%	≥95%	80-94%	<80%

6.8 Participant recruitment

Patients presenting as an emergency with PSP will be invited to participate. Potential trial participants will be identified by local teams. All potential participants will be given a Patient Information Sheet (PIS) (approved by the local Research Ethics Committee, REC) describing the study. If a patient is clinically stable and the decision has been made that pleural intervention is reasonable, it is reasonable to wait for up to 4 hours before a decision is made to randomise them in to the study

6.9 Discontinuation/withdrawal of participants

A decision by a participant that they no longer wish to continue receiving study treatment should not be considered to be a withdrawal of consent for remote follow-up. However, participants are free to withdraw consent for some or all remaining study activities at any time if they wish to do so. In accordance with regulatory guidance, data that have already been collected and incorporated in the study database will continue to be used.

6.10 Frequency and duration of follow up

A minimum clinical follow-up (within 7-10 days time) is recommended for patients managed on the ambulatory or conservative pathway to ensure patient safety.

A research visit should be conducted at day 30 day (+7 days). At this visit, the patients will undergo a chest radiograph. Note, this chest radiograph is not compulsory if pneumothorax resolution has been confirmed on chest radiograph, and there is no additional clinical indication of symptoms. Participants should complete the EQ-5D-5L questionnaire and record their pain and breathlessness using a VAS.

Participants will also be asked to complete an online EQ-5D-5L questionnaire and record their pain and breathlessness using a VAS at 48hrs and day 14. Questionnaires can be completed over the phone at these timepoints.

HES, PEDW and eDRIS data, including admitted, critical, emergency and outpatient data, will be sought to determine any further admissions and hospital contacts up to 12 months. This method of follow-up will avoid the need to follow participants prospectively, which can be challenging for this patient group who frequently do not attend. We have made the decision to censor follow-up for these outcomes early (at 6 rather than 12 months) for participants recruited in the last 3-4 months, to expedite reporting the trial findings and to reduce the costs of the trial, i.e. when the team would be largely waiting for time to elapse for these last participants.

6.11 Likely rate of loss to follow-up

In the original sample size, the attrition rate and proportion of cross-overs was set at 5% and 1%, respectively, based on outcomes from a comparable study in a similar population at a 30-day primary outcome of 4%[4]. The updated sample size was calculated based on an attrition rate of 2.5% and cross-over rate of 5%, guided by the rates seen in the first 40 randomised participants.

6.12 Expenses

There are no participant travel expenses available as no additional visits are required as a result of the research study.

7. Statistical analyses

7.1 Plan of analysis

The primary analysis will be by intention-to-treat and will follow CONSORT reporting guidelines for a superiority study. A detailed statistical analysis plan (SAP) will be written before the follow-up period concludes. Binary outcomes will be compared using a generalised linear model; risk differences and relative risk will be reported. EQ-5D-5L and VAS scores will be compared using a mixed model and patient acceptability (Likert scale) will be analysed using ordinal regression. Interactions between treatment and time will be examined and if significant at the 10% level, results will be reported separately for post-intervention time points; otherwise, overall treatment effects will be reported. Adverse events will be described.

A sensitivity analysis including any unplanned attendance at hospital that does not require an admission (and so not included in the calculation of length of time in hospital up to 30 days post-randomisation) will be performed.

7.2 Subgroup analyses

No subgroup analyses are planned.

7.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. Safety data will be reported to the DMSC at a frequency to be agreed, together with any additional analyses the committee requests. In these reports, the data will be presented by group but the allocation will remain masked.

7.4 Criteria for the termination of the trial

The trial may be terminated early on the recommendation of the DMSC or the results of another study supersede the necessity for completion of this study. The funder may terminate the trial based on the criteria outlined in section 6.7.1

7.5 Economic issues

Generic health-related quality of life (HRQoL) will be measured using the Euroqol-5 Dimensions 5-levels (EQ-5D-5L) questionnaire. The EQ-5D-5L will be administered at baseline, 48 hours, 14 and 30 days. Responses will be converted into utilities using tariffs estimated from a representative sample of the UK population[11].

Quality Adjusted Life Years. In order to keep the trial as pragmatic as possible, avoid overburdening patients with multiple questionnaires over a long-period of follow-up and in a bid to keep missing information to a minimum, EQ-5D information will not be collected past 30 days after randomisation. In RAMPP, despite best efforts to minimise missing data at follow-up, 48% (109/227) completed an EQ-5D questionnaire at 12-months. At this follow-up, 62% (67/109) reported being in perfect health, and only 17% (19/109) reported utility values lower than 0.8.

Therefore, we will extrapolate 30-day EQ-5D utility in CONSEPT to 1-year utilities using information from the RAMPP trial, which sampled patients from the same population as CONSEPT. For this, we will assess the association between 30-day and 1-year EQ-5D utility in RAMPP, adjusting for age, gender and history of pneumothorax.

Survival information collected from the trial will be combined with EQ-5D utilities to generate QALYs, the outcome measure preferred by the National Institute for Health and Clinical Excellence[12].

Healthcare resource use and costs. The perspective adopted in the economic analysis will be that of the National Health Service (NHS). For this perspective we will include the costs associated with the following healthcare resource use categories from randomisation to 12-month follow-up:

- Initial procedures for the treatment of spontaneous pneumothorax (including insertion of an ambulatory device, aspiration, standard chest tube insertion, or a combination of the latter two);
- Initial length of stay following spontaneous pneumothorax;
- Subsequent procedures for pneumothorax;
- Subsequent stays in hospital or day cases due to any reason;
- Accident and emergency (A&E) visits; and
- Secondary outpatient care visits.

Given that costs due to primary and community care visits accounted for less than 2% (£70/£4,115) of total NHS costs in RAMPP, and with no indication these will likely vary between the two treatment groups in CONSEPT, information on these will not be collected.

Costs of performing the initial and subsequent procedures to treat pneumothorax will be obtained from the micro-costing of procedures undertaken in RAMPP. All other resource will be obtained from HES. We will obtain Health Resource Group (HRG) codes for each contact recorded in HES using the latest NHS Digital HRG4+ Reference Cost Grouper. HRGs will then be mapped to NHS Reference costs, to obtain the costs of each contact. To avoid double counting the costs of procedures for pneumothorax, we will remove the procedure codes for hospitalisations with a code for treatment of pneumothorax. In sensitivity analyses, costs will be assessed using NHS reference costs only.

Wider economic costs. In RAMPP, over the 12-month follow-up, each patient reported an average of 24 (95% CI: 17 to 32) days off work, with half of these days lost in the first month of follow-up. In CONSEPT, a short questionnaire will be provided on the total number of days off work lost at 30 days post randomisation. As with utility, we will extrapolate 30-day days off work in CONSEPT to 1-year using information from the RAMPP trial. Days off work will be valued using Office for National Statistics data on mean daily earnings in the UK.

Cost-effectiveness analysis. The perspective adopted in the economic evaluation will be that of the NHS, therefore productivity losses will not be included in the base case analysis. However, in a sensitivity analysis we will assess the impact of including these costs on the cost-effectiveness results.
An economic evaluation adherent to guidelines for good economic evaluation practice will be undertaken integral to the main trial[13]. A within-trial cost-utility analysis will explore the incremental cost per QALY gained by initial conservative care of large PSP when compared to initial invasive care. Cost and effect results will be reported as means with standard deviations, with mean differences between the two patient groups reported alongside 95% confidence intervals (95% CI). Depending on the amount of missing cost (which we believe to be <5% due to the centralised follow-up) and quality of life data, missing data will be imputed using recommended multiple imputation methods[14], with results from this analysis being presented as an additional sensitivity analysis. Incremental cost-effectiveness will be calculated by dividing the difference in costs by the difference in effects. Uncertainty around the incremental cost-effectiveness ratio (ICER) will be explored using non-parametric bootstrapping[15].

8. Trial management

8.1 Trial Oversight

8.1.1 Trial Management Group

The trial will be managed by a trial management group (TMG), which will meet face to face or by teleconference for the duration of the study. The TMG will be co-chaired by the Chief Investigators (Professor Nick Maskell and Professor Najib Rahman) and will include representatives from the BTC. Other members of the research team will be invited to attend as required.

The TMG will be supported by BTC, which is a UK Clinical Research Collaboration registered Clinical Trials Units. BTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and manage the trial on a day to day basis.

8.1.2 Investigator Meetings

Investigator meetings will be held approximately every 6 months to review study progress and address any issues that arise. All team members, including all study applicants, PIs and lead research nurses will be invited to these meetings.

8.2 Day-to-day management

The study will be conducted at multiple hospitals within the UK. At each hospital, a principal investigator (PI) will be responsible for trial activities but it is envisaged that much of the work will be carried out by medical staff attending patients with pneumothorax within the hospital and by hospital research nurses, and other staff with appropriate education, training, and experience.

8.3 Training and monitoring of sites

8.3.1 Initiation Training

Each site will undergo initiation training before they are given the green light to start.

8.3.2 Site monitoring

BTC will carry out central monitoring and audit of compliance of centres specialties with the principles of Good Clinical Practice (GCP) and data collection procedures. The study database will have extensive in-built validation and the TMG will review the completeness and consistency of the data throughout the trial. BTC will not check CRFs against the data entered or against source data, unless there are good reasons to visit the site to complete a monitoring visit (e.g. the central monitoring highlights a problem).

8.4 Trial Steering Committee and Data Monitoring and Safety Committee

The Trial Steering Committee (TSC) is made up of representatives of CONSEPT TMG, and independent members to be appointed by the funders.

The Data Monitoring and Safety Committee (DMSC) consists of medical statisticians and medical experts in this field. Independent members will be appointed by the funder. The Lead applicants will be available as required.

9. Safety reporting

9.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.
Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing in-patients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

9.2 Overview

Conservative care in PSP has been recently examined in a randomised controlled trial, which found a favourable side effect profile compared to standard care (16 total adverse in 162 patients in conservative care arm, compared to 49 total adverse in in 154 in standard care arm)[5].

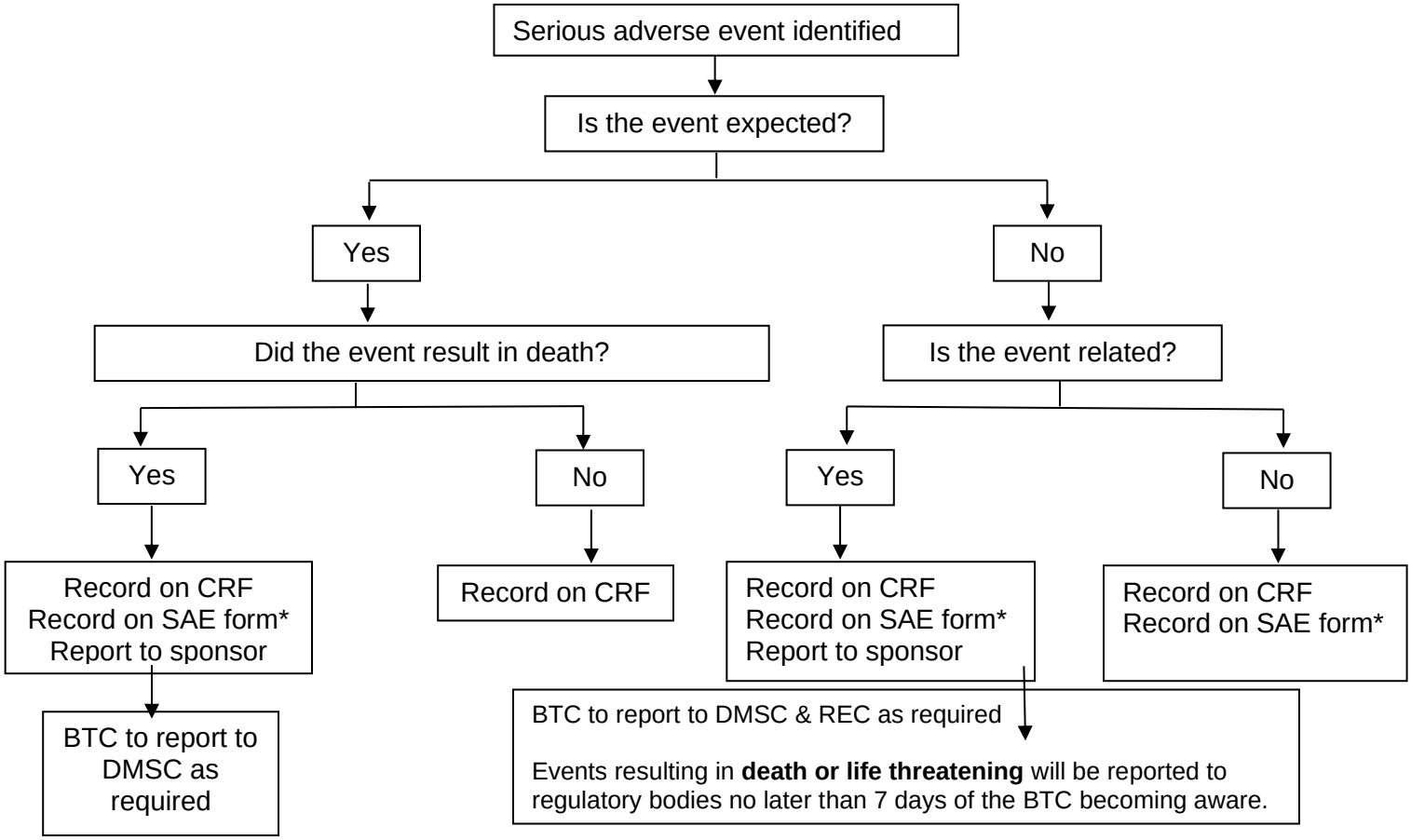
Details of all 'expected' AEs, including a description of the event and the date it started, will be recorded in the study CRFs, from the time of randomisation and for a 30 day period post randomisation.

From the time of randomisation up until 30 days post-randomisation for each study participant, centres will be required to report all fatal and 'unexpected' non-fatal SAEs to the BTC within 24 hours of becoming aware of the event. The participant will be followed-up by the research team until the event resolves or until the end of the trial if the event is ongoing. The BTC will report all of these SAEs to the trial Sponsor within the same 24 hour period. 'Expected' SAEs will not need expedited reporting to the Sponsor, unless they result in death, and will be reported periodically instead.

Further to this, BTC will report suspected unexpected serious adverse reactions (SUSARs) to the research ethics committee (REC), the DMSC and the clinical lead, and copy all reports to the Sponsor within 15 days (or 7 days, if fatal) of becoming aware of the event.

All SAEs will be reviewed by the Clinical Lead, DMSC and Sponsor as required**.**

Figure 2 Serious adverse event reporting flow chart



*To be reported within 24 hours of becoming aware of event.

9.3 Expected adverse events associated with the study interventions

The following AEs are 'expected' after the procedure and therefore do not require expedited reporting to the Sponsor unless they result in death:

- Minor Bleeding (defined as not causing haemodynamic compromise or requiring blood transfusion)
- Minor Pain (defined as settling spontaneously or controlled with analgesia)
- Breathlessness
- Subcutaneous emphysema (unless causing airway compromise or requiring surgical intervention)
- Pleural infection (unless requiring surgical intervention)
- Subcutaneous infection at drain insertion site
- Tension pneumothorax
- Unintentional removal or dislodgement of pleural device
- Requirement for further pleural procedures
- Persistent cough
- Hypotension related to procedure

- Equipment disconnection
- Topical skin reaction to chlorhexidine
- Recurrence (including requiring readmission)
- Respiratory tract infection

10. Ethical considerations

10.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA), including any provisions of Site Specific Assessment (SSA), and local site capacity and capability confirmation. Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIS and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

10.2 Risks and anticipated benefits

We believe this study does not pose any specific risks to individual participants, nor does it raise any serious ethical issues. As with all trials the main benefit of participating is an altruistic one, to improve care for subsequent patients who suffer from pneumothorax.

The trial information materials will provide clear details of the anticipated risks and benefits of taking part in the study. The risk and benefits of the study will be discussed with the participating sites as part of the process of inviting patients to take part and providing written informed consent.

10.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIS. The PIS will be thoroughly reviewed by our PPI panel for readability. Translated PILs can be made available based on site requirements to ensure accessibility of the trial. Translation services will be provided by an approved body contracted by the University of Bristol for the translation of confidential information.

10.4 Obtaining informed consent from participants

Informed consent should be obtained from each patient before enrolment into the study. Patients will be approached by an authorised member of the local research team (as specified in the delegation log). All individuals receiving informed consent will be GCP trained.

10.5 Co-enrolment

Co-enrolment with the RASPER study (IRAS 316434) will be permitted for patients enrolled in the usual care arm of the CONSEPT trial who are treated with a chest drain. Co-enrolment with other studies will be considered by a member(s) of the CONSEPT TMG on a case-by-case

basis. Generally, co-enrolment will be allowed if the intervention is not expected to influence the primary outcome and it is not considered too burdensome for the patient.

11. Research governance

This study will be conducted in accordance with:

- GCP guidelines
- UK Policy Framework for Health and Social Care Research

11.1 Sponsor approval

Any amendments to the study documents must be approved by the Sponsor, TSC and funder prior to submission to the HRA/REC/MHRA.

11.2 NHS approval

Confirmation of capacity and capability from the local NHS Trust is required prior to the start of the study at each site.

Any amendments to the study documents approved by the HRA and REC will be submitted to the Trust for information or approval as required.

11.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved by the HRA/REC/MHRA that they receive and ensure that the changes are complied with.

11.4 Monitoring by sponsor

The study will be monitored and audited in accordance with North Bristol NHS Trust's Monitoring and Oversight of Research Activity SOP, which is consistent with the UK Policy Framework for Health and Social Care Research. All study related documents will be made available on request for monitoring and audit by the sponsor (or BTC if they have been delegated to monitor see section 8.3.2), the relevant REC and for inspection by the MHRA or other licensing bodies. Some elements of monitoring will be delegated to BTC and a monitoring plan will be agreed.

11.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research if there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree

in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.6 Clinical Trial Authorisation

Clinical Trial Authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) is not required.

12. Data protection and participant confidentiality

12.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

12.2 Data handling, storage and sharing

12.2.1 Data handling

All participant data will be entered into a purpose-designed database hosted on the University of Bristol network. Database access will be password-controlled and restricted to CONSEPT trial staff at the participating site and the co-ordinating centre.

Any information capable of identifying individuals will be held on a secure University of Bristol server. CONSEPT trial staff at the coordinating centre will have access to this identifiable information. If required, this information can be securely shared with participating sites who will contact potential participants, for the purposes of the study. No personally identifiable data will be held on the study database.

The processing of personal data of participants will be minimised by making use of a unique participant trial number on trial documents and the study database, with the exception of signed consent forms and the screening log.

The database and randomisation system will be designed to protect patient information in line with data protection legislation. Study staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at participating sites and in accordance with ethics approval. All documents will be stored securely and only accessible by study staff and authorised personnel. Data will be collected and retained in accordance with data protection legislation.

Data will be entered promptly, and data validation and cleaning will be carried out throughout the study. Where electronic patient medical notes are used, local Trust policies will be followed.

Data transferred from the Coordinating Centre to the Health Economics team will also be transferred by secure means.

12.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial. In compliance with the Medical Research Council (MRC) Policy on Data Sharing, and with participant agreement, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique study identifier, will be held indefinitely. These will be retained because of the potential for the raw data to be used subsequently for secondary research and/or training.

12.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

13. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR- Health Technology Assessment programme) and through patient organisations and newsletters to patients, where available.

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Amendments to protocol

Amendment number (i.e., REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
CONSEPT REC SA1	1.0	13 DEC 2022	2.0	08 JAN 2024	1. Inclusion criteria wording changed 2. Database location changed from UHBW (NHS) server to University of Bristol (UoB) server 3. Randomisation method clarified	
CONSEPT REC SA 2	2.0	08 JAN 2024	3.0	03 APR 2025	1. Updated primary and secondary outcomes 2. Updated sample size calculation 3. Updated trial schema 4. Updated analysis plan	