TREATMENT OF HIDRADENITIS SUPPURATIVA EVALUATION STUDY

(THESEUS)

PROTOCOL V4.0_APPROVED _DATED 09.12.21

Sponsor:	Cardiff University
Sponsor ref:	**SPON 1734-19**
Funder:	**NIHR HTA (Commissioned call)**
Funder ref:	**17/98/01**
REC ref:	
IRAS number:	**IRAS Project ID: 266172**
ISRCTN/ ClinicalStudies.gov ref:	
Q-Pulse Document Template Number:	**TPL/003/2**

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations, GCP guidelines, and CTR's SOPs.

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

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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General Information This protocol describes the THESEUS clinical study and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to CTR.

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The THESEUS study is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the THESEUS Study Management Group (SMG).

For **all queries** please contact the THESEUS team through the main study email address. Any clinical queries will be directed through the Study Manager to either the Chief Investigator or a Co-Investigators.

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Glossary of abbreviations

AE	Adverse Event
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Study of Investigational Medicinal Product
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation 2016/679
GP	General Practitioner
HB	Health Board
HS	Hidradenitis suppurativa
HTA	Health Technology Assessment
IC	Informed consent
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality control
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SMF	Study Master File
SMG	Study Management Group
SSC	Study Steering Committee

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
NS04	2.1	26.03.20	To section 11.2 added: As a result of the COVID-19 crisis, follow-up processes for the participants currently in the THESEUS study need to be updated. Remote follow-ups via telephone, instead of face-face, can be conducted in order to reduce the risks to participants (ie to them contracting/ spreading the COVID-19 virus) by attending follow-up appointments in person.
NS05	3.0	29.06.20	Section 9.1: Sites who conduct a search of their patient register and identify potentially eligible patients can send these patients the participant information sheet and consent form. Ideally, the recruitment/baseline appointment should be carried out face-face, however, for those patients who are already known to the study team, eligibility and consent and the baseline appointment can be performed remotely, without the need for the patient to attend the hospital clinic. For those patients who are not known to the research team or have not been reviewed before in person by the study team (the only exceptions

			are patients with skin involvement limited to non-intimate sites such as the axilla who could be assessed remotely), they will need to attend a clinic in person to ensure eligibility and assess disease severity. Community recruitment will occur by publicity involving clinic posters and website adverts on the THESEUS study and HS Trust web sites. The websites will have contact details for a research team member at each participating site. A patient interested in taking part in the study will be asked to contact the participating site directly via these contact details. Remote recruitment means either by telephone call (plus option to upload photographs of lesions) or video call. Many Trusts are currently consulting with their patients via such remote methods and these can continue to be used in this study. Section 9.4: Where the recruitment appointment is conducted remotely, the participant will be sent the PIS and consent forms (carbon triplicate copies) via post or email. One copy of the signed consent form will be kept by the participant and the other copies returned to the research site and the CTR. Section 11.2: As a result of the COVID-19 crisis, follow-up processes for the participants currently in the THESEUS study need to be updated. Remote

			follow-ups via by telephone call (plus option to upload photographs of lesions) or video call instead of face-face, can be conducted in order to reduce the risks to participants (ie to them contracting/ spreading the COVID-19 virus) by attending follow-up appointments in person.
NSA08			Due to COVID-19, the current process of obtaining consent from participants to take part in an interview will be burdensome to the participant and to the research team. This amendment will allow for consent to be taken verbally over the telephone. Verbal consent will be recorded. Interviews will be conducted over the telephone; face-face interviews will no longer be an option.
NSA11			Section 12.1: Clarifications around what constitutes a withdrawal. If the participant wishes to switch to another THESEUS intervention or, if necessary, a non-THESEUS HS intervention, then this would not be classed as a withdrawal.

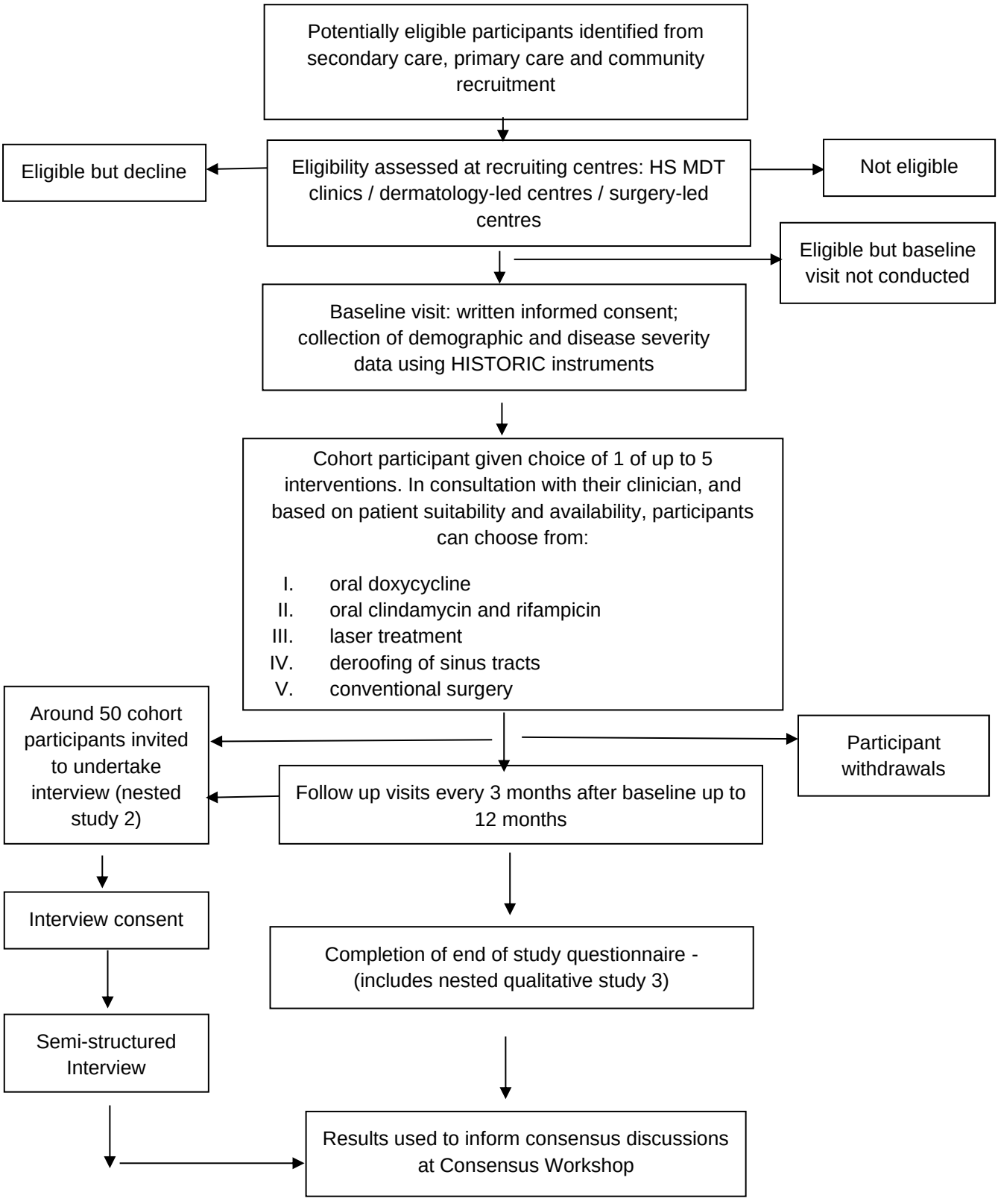
2 Synopsis

Short title	Treatment of Hidradenitis Suppurativa Evaluation Study
Acronym	THESEUS
Internal ref. no.	
Development phase	N/A
Funder and ref.	NIHR HTA (ref 17/98/01)
Study design	Prospective observational cohort study
Study participants	Adults with active Hidradenitis Suppurativa (HS) of any severity
Planned sample size	150
Planned number of sites	10 secondary care sites
Inclusion criteria	• Adults at least 18 years old with active HS of any severity • Diagnosis meets disease definition (a lifetime history of at least 5 flexural skin boils or 2 flexural skin boils in last 6 months) and confirmed by recruiting clinician with experience of HS care • HS not adequately controlled by current treatment • At least one of the five study interventions is appropriate for participant's care
Exclusion criteria	• Unable or unwilling to give informed consent • Pregnancy or breastfeeding •Not fluent in English (questionnaires are only validated in English)
Treatment duration	Up to 6 months
Follow-up duration	12 months
Planned study period	36 months
Primary objective	To inform the design of future HS RCTs and to understand how HS treatments are currently used
Secondary objectives	To determine i) feasibility of recruitment for future RCTs of HS treatments; ii) choice and characterisation of study interventions (dose of medication, type of surgical techniques used); iii) current patient pathways and understanding of what influences patients' and clinicians' treatment choices; iv) choice, feasibility and responsiveness of outcome measure instruments, including evaluation of minimum important difference (MID) to inform sample size calculations; and v) consensus-agreed recommendations for future study designs
Tertiary/Exploratory objectives	N/A
Primary outcomes	Proportion of participants who are eligible, and hypothetically willing, to use the different treatment options

Secondary outcomes	• proportion of participants choosing each of the study interventions, with reasons for their choices • proportion of participants who switch treatments during the study follow-up period, with reasons for switch • treatment fidelity • loss to follow-up rates over 12 months • efficacy outcome estimates after 6 months' of follow up to inform outcome measure instruments' responsiveness (minimum important difference, MID)
Tertiary/Exploratory outcomes	N/A
Intervention	(i) oral doxycycline 200mg OD for 6 months initially; (ii) oral clindamycin and rifampicin both 300mg BD as a combined course for 10 weeks; (iii) laser treatment; (iv) deroofing of sinus tracts; (v) conventional surgery (narrow or wide excision, with a range of closure methods)

3 Study summary & schema

3.1 Participant flow diagram



3.2 Study lay summary

Hidradenitis suppurativa (HS) is a long term, painful skin condition. It involves boils in areas such as the arm pits and groins. It affects young adults of working age. HS has a big effect on quality of life due to pain, scarring and release of pus. It also affects sex and relationships.
Our planned study will provide vital information to answer questions that were identified as priority areas for research by patients with HS and the doctors and nurses who treat them.

Aim
To inform the design of future HS trials and to understand how HS treatments are currently used. This involves five steps:

(1) Describe the treatments used around the country (particularly the type of operation, which can vary from centre to centre);

(2) See whether patients might consider joining a research study in the future and which treatment(s) they would prefer;

(3) Define how patients with HS are currently seen within the health service. Learn what influences patients' and clinicians' treatment choices;

(4) Select the best ways of measuring response to treatment (outcome measures);

(5) Ask patients and doctors to agree the best design for future HS studies.

Design & methods
The HTA wished to fund a study on "Management of HS". We have designed this study in response to the funders. Our team includes people with HS and the leader of a patients' group, skin doctors, general practitioners (GPs), surgeons and research experts. We are supported by a Clinical Trials Unit to make sure that the research is high quality. We are backed by two networks that coordinate skin doctors and plastic surgery doctors around the country.

We have already run surveys of people with HS, skin doctors and surgeons about HS treatment. From these surveys, we have picked five main treatments that future research is likely to want to compare. We will invite people with HS to join the study as volunteers. By inviting people who are treated by skin doctors and those treated by surgeons, we should receive information about a range of treatments. The volunteers will be able to pick from the range of treatments available locally and, for

the year after, we will record what happens to them. We will measure how well the treatment has worked using recommended questionnaires and will help to interpret the questionnaire results by checking what changes in score matter to patients and whether the questionnaires are suitable for normal clinical practice. During the study we will video record the surgical and laser operations to make a training video for future studies.

Patient & public involvement

The President of the HS Trust has been a member of our bid team from the beginning and will be part of the group that manages the study. She led our patient survey, using the HS Trust website and social media. The survey, completed by 358 people, helped to shape our study plan. Throughout the THESEUS study, we will interview participants about their study experiences. We will ask about reasons why they might, or might not, take part in future studies. A group of people with HS and doctors/nurses/ researchers involved in the study will meet in a workshop at the end of the study. This will be used to agree the best designs for future HS research.

Dissemination

We will present the findings from our study at international meetings of doctors and researchers. We will publish them openly in journals, where anybody can see them. The HS Trust patient support group will host links to these publications on its website, including a plain language summary and podcasts.

4 Background

Hidradenitis suppurativa (HS) is a chronic, often painful, inflammatory skin disease that affects approximately 1% of adults (1). It has a large impact on quality of life due to pain, discharge of pus, scarring and effects on sexual function and relationships. Onset is usually in early adulthood and so careers and economic productivity are often affected.

Evidence explaining why this research is needed now

Despite being a relatively common condition, the evidence base for management of HS is relatively sparse, as highlighted in the Cochrane review first-authored by the lead applicant (2). Only 12 RCTs with a total of 615 participants were identified. European treatment guidelines are largely based on consensus as a result (3), yet surveys of dermatologists and surgeons conducted by team members have demonstrated idiosyncrasies in treatment strategies by different clinicians, suggesting that there may be undesirable variation in treatment in the UK. To prioritise the large HS research gaps, the lead applicant co-ordinated the HS James Lind Alliance Priority Setting Partnership (PSP), which published a top 10 list of future research priorities including both medical and surgical interventions (4). Our proposal incorporates several HS PSP priorities, including investigation of oral treatments, which was the number one priority, and surgical studies, covered by the sixth and eighth priorities.

Traditionally, there has been a lot of heterogeneity in outcomes across HS studies (5). The funding call from the HTA has come at an opportune time for HS research because core outcome domains have been established by the HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC) (6, 7). The lead applicant is a member of the HISTORIC Steering Committee and so is well-placed to integrate this application with HISTORIC's ongoing work, which involves patients and clinicians in both Europe and North America. Our proposal meets all aspects of the Commissioning Brief by investigating second-line interventions for HS (both medical and surgical) in a prospective cohort study. The cohort study has been designed according to the IDEAL 2b framework for the evaluation of surgical interventions. Stage 2b, refers to the exploration stage in evaluating new surgical techniques and this will be with regard to the development of deroofing as an intervention for HS in the UK. We will work closely with HISTORIC to define outcome measurement instruments to assess treatment response and will provide estimates of Minimal Important Difference (MID) for each.

Recommendations for future primary research will be formulated in a consensus workshop attended by study participants, clinicians and researchers.

In addition, our proposal includes a nested qualitative study that will further characterise the interventions used in the cohort study and help to understand patients' and clinicians' perspectives in making informed treatment choices. Its objectives are to (i) characterise and document best practice in delivering the study interventions, (ii) understand barriers and facilitators to recruit into future HS randomised controlled trials (RCTs), and (iii) understand patients' perspectives on treatment choices.

Particular focus will be given to characterising the surgical and laser interventions, and training videos will be produced to inform development of suitable training packages for use in future RCTs. The videos are part of laying the groundwork for quality assurance in a phase III study, following the IDEAL Stage 2b approach (http://www.ideal-collaboration.net/about-ideal/exploration/).

4.1 Rationale for current study/Justification of treatment options

Informed by the requirements of the National Institute for Health Research Health Technology Assessment (NIHR HTA) Commissioned Funding Call, the THESEUS study includes: (i) a non-randomised, non-CTIMP prospective cohort study with 12-months' follow-up, supported by a bespoke and repeatable training package; (ii) nested mixed methods and process evaluation studies; and (iii) a consensus workshop to agree key design features of future RCTs of HS treatments.

The cohort study has been designed according to the IDEAL 2b framework for the evaluation of surgical interventions. The IDEAL framework outlines a process of 'innovation, development, exploration, assessment, and long-term study' (8). Stage 2b, refers to the exploration stage in evaluating new surgical techniques.

Our research plan is informed by surveys sent to HS patients (n=358), dermatologists (n=57) and plastic and general surgeons (n=225). The UK dermatologists survey is an update of a previous version published in 2015 (9).

PROSPECTIVE COHORT STUDY (0 to 36 months)

Health Technologies being assessed:

(i) oral doxycycline 200mg OD (this is likely to be a standard care comparator for many future RCTs);

(ii) oral clindamycin and rifampicin both 300mg BD as a combined course for 10 weeks (commonly used second-line intervention, when first-line oral therapy has failed);

(iii) laser treatment (recommended in the European HS Guidelines but not widely used for HS in the UK) (3);

(iv) deroofing of sinus tracts (again recommended in the European Guidelines but very uncommon in the UK) (3, 10);

(v) conventional surgery (narrow or wide excision, with a range of closure methods).

Choice and dose of study interventions has been informed by results of our stakeholder surveys. Oral doxycycline and clindamycin solution are standard treatments, as well as the combination of oral rifampicin and clindamycin for 10-12 weeks. However, there is a great deal of variation in both surgical and medical approaches.

Hair-removal laser treatment and deroofing of sinus tracts are not standard treatments in the UK, but they are both included in the summary recommendations of the European Dermatology Forum HS guidelines (3).

Hair removal is performed by individuals trained and certified in the use of medical lasers (clinicians or NVQ level 3 certified individuals), and it is believed that only limited use in people with HS in the UK may be due to underuse of referral pathways to allow patients to access laser treatment. Training in laser treatment is already formalised as part of medical laser training. Certification is required for individuals to be insurable. Providing formal training in laser treatment within this project is not necessary, however a laser protocol will be provided.

Deroofing uses standard surgical equipment and transferable skills that will already be possessed by surgeons and some dermatologists (10). However, there is limited awareness of the technique in the UK, which is likely to account for its low uptake.

Each study site will offer at least 4 of the 5 interventions.

5 Study objectives/endpoints and outcome measures

5.1 Primary objectives

To inform the design of future HS RCTs and to understand how HS treatments are currently used.

5.2 Secondary objectives

To determine:

i) feasibility of recruitment for future RCTs of HS treatments;

ii) choice and characterisation of study interventions (dose of medication, type of surgical techniques used);

iii) current patient pathways and understanding of what influences patients' and clinicians' treatment choices;

iv) choice, feasibility and responsiveness of outcome measure instruments, including evaluation of minimum important difference (MID) to inform sample size calculations; and

v) consensus-agreed recommendations for future study designs.

5.3 Primary outcomes measure(s)

Proportion of participants who are eligible, and hypothetically willing, to use the different treatment options.

5.4 Secondary outcomes measure(s)

- proportion of participants choosing each of the study interventions, with reasons for their choices
- proportion of participants who switch treatments, with reasons for switch
- treatment fidelity
- loss to follow-up rates over 12 months
- efficacy outcome estimates after 6 months' of follow up, post treatment, to inform outcome measure instruments' responsiveness (minimum important difference, MID)

6 Study design and setting

PROSPECTIVE COHORT STUDY (0 to 36 months)

The setting is secondary care, including dermatology departments, plastic and general surgery departments, and HS multi-disciplinary clinics. Community recruitment is also planned because of the average seven-year delay before HS diagnosis (13) and based on the experience of successful recruitment using community advertising for the NIHR-funded Hi-Light study in vitiligo (14) - another condition that is often neglected by health services. 150 participants will be recruited.

Participants will be asked to select one of the treatment options detailed in section 4.1 that is appropriate for their care. The clinician will advise the participant on which treatments are most suitable and available to help guide their treatment choice. If a site is unable to offer the chosen treatment, it may be possible for the participant to attend a neighbouring hospital site to receive that treatment, subject to local arrangements. If on discussion with their clinician the participant prefers another treatment outside of the study treatments being offered by the recruiting site they will not be recruited and their reason(s) for preferring another intervention will be recorded in the screening log. No randomisation is necessary for this prospective cohort study. If the participant's first choice is an intervention for which the waiting time at their centre is a significant time, they will be offered treatment to cover the interim period based on the joint decision between the clinician and the participant. The interim treatment would preferably be one of the study interventions, however, other treatments are permitted depending on clinician judgement. Participants will be allocated to their chosen treatment interventions and followed-up for a period of up to 12 months. The clinical effectiveness outcomes will be assessed at 6 months following the time the patient made their intervention choice. Once the participant has been on the chosen intervention for 6 months they will be free to choose alternative treatment options or combinations of treatments as required. Follow-up will be continued for up to a further 6 months.

No formal training will be provided for conventional surgical options, as the objective of the cohort study is to document variability in current practice. The surgical technique used for each procedure will be carefully documented and some basic parameters will be included in a protocol which allows for wide variation in practice. Choice of laser for hair removal treatment will be dictated by the participant's skin type and the laser(s) available at the recruiting centre.

The deroofing intervention is not currently offered as standard treatment in the UK. In keeping with the Ideal stage 2b framework, a bespoke training package will accelerate surgical innovation by fast-

tracking the application of surgeons' existing skills. An in-person training session between the potential early adopters (surgeons recruiting into the study) and innovators (a UK deroofing expert) will take place at the beginning of the THESEUS study (11). The training materials will be made available on the Reconstructive Surgery Studies Network website, so that surgeons who were not available to attend can still access the training.

Feedback on the training event will be sought from attendees, so that it can be modified and then re-used before a definitive study. The edited videos of procedures can be used more widely to support the diffusion of innovation as part of the outputs of the proposed project. Continuing Professional Development points will be sought from the Royal College of Surgeons of England for those undergoing the training.

7 Site and Investigator selection

This study will be carried out at 10 participating secondary care sites within the UK. Sites will be selected from those that offer a multidisciplinary team (MDT) approach integrating HS medical and surgical care, those that have particular experience in HS surgery, and those that have a dermatology department that is experienced in HS medical management. All sites who are interested in participating in the study will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the study.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the THESEUS Study email account (see contact details on page 4):

- The confirmation of capability and capacity letter from the site's R&D Department
- Favourable opinion of host care organisation/PI from Main Ethics committee
- A signed Study Agreement
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- A copy of the most recent approved GP letter on host care organisation headed paper
- Returned copy of the Self-Evident Correction Log signed by the PI.

Upon receipt of all the above documents, the Study Manager will send written confirmation to the Principal Investigator and lead Research Nurse detailing that the centre is now ready to recruit participants into the study. This letter/email must be filed in each site's Investigator Site File (ISF). Along with the written confirmation, the site should receive a study pack holding all the documents required to recruit into the Study.

Occasionally during the study, amendments may be made to the study documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain REC and local R&D approval for the new documents.

Site initiation will be by attendance at a national THESEUS launch meeting or by teleconference if attendance of key personnel is unfeasible.

8 Participant selection

Participants are eligible for the study if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Study Manager before registration.

8.1 Inclusion criteria

- Adults at least 18 years old with active HS of any severity
- Diagnosis meets disease definition (a lifetime history of at least 5 flexural skin boils or 2 flexural skin boils in last 6 months) and confirmed by recruiting clinician with experience of HS care
- HS not adequately controlled by current treatment
- At least one of the five study interventions is appropriate for participant's care

8.2 Exclusion criteria

- Unable or unwilling to give informed consent
- Pregnancy or breast feeding
- Not fluent in English (questionnaires are only validated in English)

9 Recruitment, Screening and registration

9.1 Participant identification and recruitment processes

Participants will be identified by Principal Investigators (PIs), co-investigators and research nurses within the secondary care setting. Identification may involve reviewing or screening the identifiable personal information of participants and if so this will be undertaken by members of the normal clinical team. Sites who conduct a search of their patient register and identify potentially eligible patients can send these patients the participant information sheet and consent form. Ideally, the recruitment/baseline appointment should be carried out face-face, however, for those patients who are already known to the study team, eligibility and consent and the baseline appointment can be performed remotely, without the need for the patient to attend the hospital clinic. For those patients who are not known to the research team or have not been reviewed before in person by the study team (the only exceptions are patients with skin involvement limited to non-intimate sites such as the axilla who could be assessed remotely), they will need to attend a clinic in person to ensure eligibility and assess disease severity. Consent would be obtained at this visit and the baseline appointment conducted. Participants may also be recruited through Participant Identification Centres (PICs), for example primary care PICs. Community recruitment will occur by publicity involving clinic posters and website adverts on the THESEUS study and HS Trust web sites. The websites will have contact details for a research team member at each participating site. A patient interested in taking part in the study will be asked to contact the participating site directly via these contact details. Only a member of the participant's existing clinical care team will have access to participant records without explicit consent in order to identify potential participants and check whether they meet the inclusion criteria. The initial approach to participants will be made by a member of the participant's existing clinical care team, except when there is no existing care team and the participant is responding to a study advertisement. Eligibility of participants will be assessed by clinicians.

Remote recruitment means either by telephone call (plus option to upload photographs of lesions) or video call. Many Trusts are currently consulting with their patients via such remote methods and these can continue to be used in this study.

9.2 Screening logs

A screening log of all ineligible and eligible but not consented/not approached patients will be kept at each site so that any biases from differential recruitment will be detected. These screening logs will

contain patient identifiers, for example, patient initials and/or date of birth. The screening log should be sent to the THESEUS study email address every month.

9.3 Recruitment rates

A total of 150 participants will be recruited at an expected rate of 1-2 per month per site.

9.4 Informed consent

Please refer to section 9.1 for participant identification and recruitment processes. Where the recruitment appointment is face-face, consent will be taken by suitably qualified PIs, co-investigators and research nurses. Participants will receive the current version of the Participant Information Sheet (PIS) prior to the consent process and will be given plenty of time to ask questions relating to the PIS and other elements of the study prior to consent being taken. Where the recruitment appointment is conducted remotely, the participant will be sent the PIS and consent forms (carbon triplicate copies) via post or email. One copy of the signed consent form will be kept by the participant and the other copies returned to the research site and the CTR. Participant care will remain paramount at all times.

Specific consent will be requested from participants to be involved in the interview component of the study (See section 13.1.2 for consenting process). Interviews with participants will be carried out by researchers based at Nottingham University. Consent for these elements is not required in order to participate in the cohort study (ie. taking part in an interview is optional). Participants who are invited to attend the consensus workshop will not be asked formally for their consent, as their attendance will provide implied consent. Participants who are invited to attend the workshop may or may not have taken part in the interview component of the study.

Consent will be sought to contact participants at the end of the study regarding opportunities to participate in future HS research studies.

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study. Only when written informed consent has been obtained from the participant and they have been enrolled into the study will they be considered a study participant.

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We will comply with Welsh language requirements and the PIS, Consent Form and any other required participant documentation will be available in Welsh. However, all documentation used for data collection (i.e. outcome measures) will remain in English as they are designed and validated in English.

The right of the participant to refuse to participate in the study without giving reasons will be respected. After the participant has entered the study, the investigator will remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the study for the purpose of follow up and data analysis. Similarly, the participant will remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

9.5 Registration and Randomisation

9.5.1 Registration/baseline

Suitable participants who have provided written informed consent will be enrolled into the study and will be registered by recording key information including; contact details, past medical and medication history, as well as demographics, and will choose one of the five preferred interventions, in consultation with their clinician.

9.5.2 Randomisation

There is no randomisation element in this study.

10 Study Intervention

10.1 Specified interventions

i) Oral doxycycline 200mg OD for 6 months, with the option to continue for up to a further 6 months or switch to another intervention or combination of interventions after the participant has been on their chosen intervention for 6 months;

(ii) oral clindamycin and rifampicin both 300mg BD as a combined course for 10 weeks, with the option to continue up to 6 months and thereafter switch to another intervention or combination of interventions after the participant has been on their chosen intervention for 6 months;

(iii) laser treatment using nd-YAG laser (skin types 2-6) or Alexandrite/ diode laser (skin types 1-3) administered on 4 occasions each one month apart, with the option to receive another intervention or combination of interventions 6 months after the first laser treatment and for up to a further 6 months;

(iv) deroofing of sinus tracts using electro-cautery (optimal protocol to be determined by UK expert and provided to centres as a training package including a video). It is expected that by following this training video that healthcare professionals, including; dermatologists, plastic surgeons and other surgeons will be able to perform this procedural intervention. The procedure is carried out under local anaesthetic. , repeated during the next 6 months if necessary and with the option to receive another intervention or combination of interventions 6 months after the initial deroofing treatment and for up to a further 6 months. The total area treated at one time is limited by the volume of local anaesthetic needed and expected degree of impairment of activities of daily living during recovery;

(v) conventional surgery (narrow or wide excision, with a range of closure methods depending on the preference of the clinician), with the option to receive another intervention or combination of interventions 6 months after the surgery and for up to a further 6 months.

11 Study procedures

The duration of participant involvement in most cases will be up to 12 months. Efficacy of interventions will be assessed at 6 months following their baseline appointment (when they make their intervention choice) and then participants are free to switch to another intervention or combination of interventions after the participant has been on their chosen intervention for 6 months. Participants who opt for an intervention that has a significant delay before receipt of that intervention can opt to have another intervention during that wait time. If a site is unable to offer the intervention chosen by the patient, it may be possible for them to attend a neighbouring study site, subject to local arrangements. Some participants will attend the consensus workshop that will take place at a point during the final year of the study.

Study assessments will entail a clinical history, completion of questionnaires and a clinical examination. These assessments will take place at baseline and every 3 months following baseline up to 12 months post baseline (see figure 1).

We will collect information about potential confounders including body site, baseline disease severity (measured by Hurley staging) (12), previous treatment received, smoking and body mass index. We will also record if participants are referred to additional services to support the management of HS (e.g. weight-loss, smoking cessation and psychological resilience programmes).

11.1 Assessments /Data collection

The schedule of assessments is summarized in figure 1. A window of 2 weeks is permissible either side of the intended follow up date. Safety blood tests (full blood count, renal function, liver function) will be required at baseline and after 4 weeks only for participants choosing the clindamycin and rifampicin intervention. These blood tests are part of usual care and will be carried out within the hospital setting. The participants treating clinician within secondary care will review the blood results and inform the participant whether they can start/continue with their chosen clindamycin and rifampicin intervention.

Efficacy outcome measures will include the six core domains recommended by the HISTORIC core outcome set initiative for HS: (i) Pain (using a numeric rating scale) (ii) HS-specific quality of life (HiSQOL), (iii) global assessment, (iv) progression of course (flare frequency), (v) physical signs and (vi) symptoms (drainage resulting in need for dressings and fatigue) (7). HISTORIC-recommended instruments will be employed where these are available, plus a generic measure of quality of life (EQ-5D). We will report completeness of each outcome at each time point.

Pain NRS will be measured at the baseline appointment and then on a daily basis for the first 12 weeks following treatment commencement via mobile telephone text message.

Figure 1. Schedule of interventions and assessments

Review number	-1	0	1	2	3	4
Planned month	-1	Baseline	3	6	9	12
Screening logs	X	X				
Eligibility assessment	X	X				
Demographics and consent		X				
Clinical examination including Hurley stage		X	X	X	X	X
Interventions for which participant is potentially eligible		X				
Intervention received, with reasons for choice (including treatments switched after baseline)		X	X	X	X	X
Outcomes						
HS quality of life questionnaire (HiSQOL)		X	X	X	X	X

Dermatology Life Quality Index (DLQI)		X	X	X	X	X
EQ5D-5L questionnaire		X	X	X	X	X
Pain visual analogue scale (VAS/NRS)		X	X	X	X	X
Pain score (via text message)		12 weeks from start of intervention				
Need for dressings		X	X	X	X	X
Fatigue questionnaire		X	X	X	X	X
Patient global assessment		X	X	X	X	X
Anchor question for change in severity			X	X	X	X
Flares		X	X	X	X	X
Assessment of HS physical signs		X	X	X	X	X
Adverse effects of study treatment			X	X	X	X
Treatment fidelity			X	X	X	X
End of study questionnaire (participants and clinicians)						X
Surgeon questionnaires/pro-forma		After each surgery				
Structured interview (subset of participants)		Single interview				
Consensus workshop (subset of participants, clinicians and researchers)		Single workshop				

Surgeons will be asked to complete a brief questionnaire to document the techniques used, any problems encountered, and resources used after each surgery.

Participants and recruiting clinicians/surgeons will complete an end-of study questionnaire as part of the nested mixed methods studies to assess satisfaction with treatment and barriers and facilitators to participation in future RCTs. (see section 13).

11.2 Follow-up

Follow up assessments will be conducted according to the schedule shown in Figure 1. As a result of the COVID-19 crisis, follow-up processes for the participants currently in the THESEUS study need to be updated. Remote follow-ups via by telephone call (plus option to upload photographs of lesions)

or video call instead of face-face, can be conducted in order to reduce the risks to participants (ie to them contracting/ spreading the COVID-19 virus) by attending follow-up appointments in person. Capturing a daily pain score from participants will be via a daily text message being sent to the participant's mobile phone for the first 12 weeks commencing when the participants begin treatment. A mobile communications provider will be used to send reminder text messages every day to the participants. They will enter their pain score (between 0 – 10) directly in the text message. When they click reply this data will automatically be uploaded onto the Theseus study database. After the initial 6 months when participants are asked to continue within one intervention arm if possible, there will be up to 6 months of follow up. During the follow up phase, participants are able to continue their current intervention or switch to another intervention or combination of interventions.

12 Withdrawal & lost to follow-up

12.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the study.

If a participant initially consents but subsequently withdraws from the study, clear distinction will be made as to what aspect of the study the participant is withdrawing from, including:

- Withdrawal from intervention prior to 6 months' efficacy time point
- Partial withdrawal from further data collection (e.g. some of questionnaires, clinical assessments)
- Complete withdrawal from further data collection
- Withdrawal from interview study or consensus workshop

The withdrawal of participant consent shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

A participant may withdraw or be withdrawn from study intervention for the following reasons:

- Intolerance to intervention
- Pregnancy occurs whilst taking a contraindicated antibiotic
- No longer wants to continue with the study data collection processes

If the participant wishes to switch to another THESEUS intervention or, if necessary, a non-THESEUS HS intervention, then this would not be classed as a withdrawal. Instead, this switch should be recorded on the review 1/2/3/4 intervention forms at the participant's next review. If the switch is due to adverse events, this should be recorded on the adverse event form.

In all instances participants who consent and subsequently withdraw will complete a withdrawal form (see Withdrawal Form in study pack) or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal form should be sent to THESEUS study team (THESEUS@cardiff.ac.uk). Any queries relating to potential withdrawal of a participant should be forwarded to the THESEUS study manager (THESEUS@cardiff.ac.uk). If a participant requests not to be contacted by text message every day (daily pain score), they can indicate this on their withdrawal form. The THESEUS data manager will notify the text messaging company to delete the participant's mobile phone details from their records. The participant will also have the option to click STOP within their phone text massage to indicate withdrawal from this aspect of the study.

Participants will not be replaced in the study in the event of withdrawal.

12.2 Lost to follow up

Participants who do not attend for a scheduled follow up visit and who do not answer study team attempts to contact them by telephone, letter and/or e-mail will be identified as lost to follow up.

13 Nested Qualitative Study -Data Collection

13.1 Nested process and qualitative studies

Aim:

To provide detailed insight about clinical processes as well as clinician and patient perspectives of HS treatments to inform future HS research.

Objectives:

1. To characterise and document surgical and laser interventions as used during the cohort study.
2. To understand barriers and facilitators to recruitment into future clinical studies of HS treatments.
3. To understand patients' perspectives on treatment choices and the implications of these choices for patients' lives.

Methods:

Three nested studies will run within the cohort to provide complementary insight about HS and its treatment.

13.1.1 STUDY 1 - Characterising surgical and laser treatments for HS.

SAMPLE. Up to five purposively selected recruiting centres will take part in this study. Centres will be selected to reflect possible variations in service organisation and clinical expertise – i.e. we will include at least one centre led by a plastic surgeon, one led by a dermatology surgery lead, and one with a multi-disciplinary team for HS management.

DATA COLLECTION. Centres will be encouraged to use the full range of surgical techniques and procedures being considered in this study. On each occasion where a conventional surgical or laser surgical approach is used the lead surgeon/clinician will be asked to complete a simple pro-forma which details the technique used, duration of procedure, adaptations to the procedure, and resources utilised.

The increased availability of (affordable) wearable video technology makes recording procedures in surgical settings feasible (18) and a small number of procedures (n=10 per procedure) will be video recorded for review. Only procedures where consent for photography has been achieved will be recorded, and no audio recording will take place to protect anonymity.

DATA ANALYSIS. Completed pro-forma forms will be reviewed by the study team to characterise each procedure and to chart the learning curve of any new procedure being used in a centre. Characterisation will summarise key features of each procedure, such as surgical margins used, closure techniques, types of dressings etc.

Following the characterisation of each procedure an expert panel will review the video recordings to identify which (in whole or part) typify best practice.

OUTPUT. This study will provide insight into the variability of techniques used and the challenges associated with each.

Exemplar videos to illustrate best practice will be selected and a voice over describing detailed instruction about the procedure added to each; these will form a valuable training resource for future practice and research.

13.1.2 STUDY 2 - Stakeholder perspectives on HS treatment and research (an interview study)

SAMPLE. Our PPI consultation has reinforced the value of talking to stakeholders about the treatment of HS, stressing the complex journeys of diagnosis and treatment that many experience.

Approximately one-third of cohort participants (up to 50 participants) and one clinician per recruiting site (n=10) will be invited to participate in semi-structured interviews. A member of the research team will contact participants to arrange a time to interview them, over the telephone. Due to the COVID-19 pandemic, participants will not have the option for a face-face interview.

Purposive sampling of cohort participants will ensure that more patients exposed to invasive procedures (conventional surgery, de-roofing, and laser treatments) will be interviewed than those exposed to medical management (30/20). Sampling will also ensure variation in age, gender, ethnicity, HS severity and geographic location.

Each recruiting centre will nominate one clinician for inclusion in this study, ensuring a balance of dermatology and surgical colleagues.

DATA COLLECTION. Telephone interviews with participants will take place throughout the cohort study and engage with them at different points in their involvement. Interviews will focus upon their choice of treatment and factors informing this; their experience of the study treatment(s); their satisfaction with treatment; hypothetical willingness to be randomised into a future RCT and, their experience of research processes. Our PPI contributors have warned that a more discursive

consideration of HS and its impact may not be appropriate here, potentially introducing sensitive or emotional issues that are not directly relevant to aims and objectives of this research.

Interviews with clinicians will focus upon their management of HS; service delivery issues associated with different treatment options; willingness to randomise to the different treatment options; and recommendations for future HS clinical studies.

Participants will be consented separately into this nested study. Due to the COVID-19 pandemic, remote consent is needed for this aspect of the study. Participants who have expressed an interest in taking part in an interview (as indicated in the main cohort consent form) will receive a telephone call or email from a member of the research team. The researcher will ask participants to provide or confirm their email address, and they will provide the participant with the Interview Participant Information Sheet and a copy of the Interview consent form via email. If a participant is happy to take part they will be consented over the telephone; this process will be audio recorded.

A structured schedule will be used to ensure a focus upon issues pertinent to the cohort study, and all interviews will be audio-recorded and transcribed in full. All patient interviewees will be signposted at the end of the interview to online help and resources should the interviews cause any concern or upset.

DATA ANALYSIS. All data will be charted to a pre-defined thematic framework (15, 16) which will include matrices for HS treatment (to include reasons for treatment choice and satisfaction with treatment) and HS research (to include reflections on current study and recommendations for future research). Charted data will be synthesised and themes and sub-themes interpreted and summarised.

OUTPUT. Insight generated here will illuminate participants' experience of various study treatments and any manifest preference for particular treatment options (or those factors that may inform their preferences). Analysis of interview data will also provide recommendations for the nature and form of future HS clinical studies.

13.1.3 STUDY 3 - Stakeholder perspectives on HS research (survey research)

SAMPLE. All participants in the cohort study. All recruiting clinicians.

DATA COLLECTION. Free-text response questions will be added to the cohort questionnaire instruments used at 12 months to consider satisfaction with treatments, barriers and facilitators to participating in research, and treatment choice (and factors in this).

An end of study questionnaire for recruiting clinicians will include free-text response questions about barriers and facilitators to engagement in future clinical studies of HS treatment.

DATA ANALYSIS. All data will be charted to the pre-defined thematic framework used in STUDY 2. Charted data will be synthesised with data from STUDY 2 and themes and sub-themes interpreted and summarised.

OUTPUT. Recommendations for the nature and form of future clinical studies in HS. Recommendations about processes and strategies that will support the success of future clinical studies in HS.

13.1.4 Consensus workshop

Aim:

To achieve consensus amongst key stakeholders over priority research questions and proposed study designs for future research into HS

Objectives:

1. To identify up to three specific research questions suitable for future randomised controlled trials.
2. To agree key elements of the design including participants and setting, intervention, comparator and outcomes.

Methods:

SAMPLE. A maximum of 40 key stakeholders will take part with a balance between patient and clinician participants sought.

Participants will represent a range of clinical perspectives (including dermatologists, surgeons, general practitioners, nurses, commissioners), lay perspectives (including participants from the cohort study and carers/partners of people with HS), and research perspectives (including medical statisticians and clinical researchers).

PROCESS. A 1½ day consensus meeting will take place after completion of the cohort study and associated nested studies. Results from all studies (cohort, mixed methods, and outcome validation studies) will be presented. This information will be used to inform discussions over preferred study design and priority research questions. Standard consensus techniques will be used - similar to the methods used during James Lind Alliance Priority Setting Partnerships and core outcome set initiatives. This will involve adapted nominal group techniques, which incorporate whole and small group discussion to establish ranked priorities, and whole group voting as necessary. In this way we

will prioritise topics for future RCT comparisons. A private break-out room will be provided for patient-participants as necessary, so that they can manage their health needs (e.g. change dressings) and take some time-out of the conversations if needed.

There will be an opportunity to discuss decisions informally at the end of Day 1, which will allow time for wider debate and reflection, prior to the more detailed study design discussion to be held on Day 2.

DAY 1: An update on the findings of the THESEUS study will be presented, along with key background information about the previous James Lind Alliance Priority Setting Partnership results, and latest findings from the HISTORIC core outcome set group.

Facilitated, small group discussion will (i) seek to select treatments and comparators for inclusion in future research, and (ii) rank these according to importance. Whole group discussion will consider and synthesise small group rankings to produce a combined list of priority interventions and comparators to be evaluated in future RCTs -up to three priority research questions will be prioritised for further development during Day 2.

DAY 2: Working in 2-3 small groups with a mixture of stakeholders per group, we will formulate the key design elements of the prioritised study(s). This will include agreement over participants and setting; interventions (choice of interventions and comparators, type, dose and duration of medical interventions, type of surgery and degree of standardisation/training required for surgical interventions); and outcomes (primary and secondary outcomes, MID, duration and frequency of follow-up). The group will be asked to reflect on the practical challenges of delivering the proposed study, and will be encouraged to think of efficient study designs to answer the prioritised questions.

Whole group discussion (and where necessary voting) will synthesise proposals and finalise the research recommendations.

A final plenary will present the decisions of each small group to the whole group and will provide an opportunity to consider strategies to promote the refined research questions.

Throughout the workshop, experienced, independent facilitators from the UK Dermatology Clinical Studies Network will manage these processes and will ensure that all voices are heard in both the smaller and larger group interactions.

OUTPUT. An agreed list of up to three specific research questions for future research. Agreement over key design elements of the proposed future studies.

14 Safety reporting

The Medicines and Healthcare Products Regulatory Agency (MHRA) have approved a notification that a Clinical Trial Authorisation (CTA) is not required for this study, meaning THESEUS is a non-CTIMP study.

Safety reporting within this study will follow usual care pathways, as THESEUS is an observational study. Investigators will follow their usual processes of reporting adverse events, for example, yellow card reporting when required. There is no requirement to notify the research team in any expedited way of any adverse events.

The research team will collect data on any adverse events that occur during the treatment and follow-up stages of the study via routine data collection at the scheduled follow-up appointments.

14.1 Contraception and pregnancy

Clinicians will follow usual practice when administering clindamycin or rifampicin, advising the participants of the need for a highly effective method of contraception.

Of note, the BNF recommends against the use of combined oral contraceptives if rifampicin is used for longer than 8 weeks. If pregnancy occurs, clinicians are to follow usual management strategies. If the participant wishes to switch to another treatment intervention, then they can do so. Or if they wish to withdraw from the study then the withdrawal processes as outlined in section 12 should be followed.

15 Statistical considerations

15.1 Sample size

With a sample size of 150, we will be able to estimate the proportion of participants who are hypothetically willing and eligible to be randomised in a clinical study to within a 95% confidence interval of ± 7%. We also wish to identify the case-mix of patients for each of the possible treatment options. From our patient survey, the least favourable treatment option (with 13%) was minor surgical operations, which would include deroofing of sinus tracts. 150 patients will provide us with 20 patients

opting for this non-medical intervention, which is sufficient to explore delivery in the IDEAL 2b evaluation.

15.2 Missing, unused & spurious data

Detail provided in the Statistical Analysis Plan (SAP), the data management plan and the qualitative analysis plan.

15.3 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

15.4 Termination of the study

While it is preferable for participants to remain within the intervention arm that they originally chose for the initial 6-month period, they may choose to discontinue or switch interventions at any time during the study. Reasons for switching treatment will be carefully documented.

There are no specific stopping rules for the entire study because participants are free to choose their intervention in consultation with their clinician.

15.5 Inclusion in analysis

All enrolled participants will be included in the analysis. In the event of withdrawals, data up to the point of withdrawal of consent will be used.

16 Analysis

16.1 Main analysis

We will describe the willingness of patients to be recruited overall and by patient intervention stated preferences and treatment uptake, including estimating intra-cluster correlation coefficients to explore clustering by centre. The group membership of each intervention will be described using descriptive statistics using data collected at baseline (month 0) (including demographics, clinical examination). Over the study period, we will report whether patients continue with and adhere to

their chosen intervention or whether they switch to alternative HS interventions during the study period. Treatment fidelity will be defined differently for each intervention option (e.g. oral clindamycin and rifampicin both 300mg twice daily for 10 weeks vs a one off surgical intervention) and will be described over the follow-up period. Within an intervention option, and where there is variation in fidelity, we will explore the possible predictors using regression modelling.

Where a patient switches intervention, we will report the reasons for this and again explore the possible predictors of switching (including intervention type, site, and other baseline demographics). Rates of loss to follow-up over the study period will be reported and we will examine whether there are any particular characteristics associated with response at 6 months.

Average change over time will be estimated for each efficacy outcome for each group with 95% confidence intervals. We will estimate the clustering/variability between surgeons/treating clinicians. Potential confounders of outcome will be assessed using regression methods.

Global assessment will be used as our anchor tool to allow estimation of MID. This will be used to dichotomise outcomes into those with clinically meaningful change and those without clinically meaningful change (stable or worse). Receiver operating characteristic curves will be generated, and the area under the curve (AUC) calculated as a measure of the outcome's ability to detect clinically relevant change. Youden's J index will be used to determine the minimal important change (MIC), and the MID will be calculated as the difference between the mean change in the improved and stable subgroups (17).

16.1.1 Sub-group & interim analysis

Additional exploratory quantitative analysis may be undertaken based on the findings of the qualitative studies (see below). No interim analyses are planned.

16.2 Qualitative analysis

Data from the qualitative studies will be assessed using framework analysis (15, 16).

17 Data Management

Study data	Source Data				
	CRF	Participant medical notes	Text message	Site file	Questionnaire
Medical History		X			
Concurrent Medications		X			
Pain score	X		X		
Other patient-reported efficacy outcomes	X				X
Physician-reported efficacy outcomes	X				
Adverse events		X			

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

17.1 Source Data

The source data for THESEUS study will be from a variety of sources. Data will be collected using an electronic system with paper CRF as a backup (eg in the case of failure to connect to the electronic system).

Training for completion of study CRFs will be provided to the appropriate study staff prior to study commencement at site initiation.

17.2 Completion of Case Report Forms (CRFs)

17.2.1 Electronic CRFs

Data will be captured using a custom-built web-based data collection portal. This is a secure encrypted system accessed by an institutional password and complies with the General Data Protection Regulation 2016/679. The system can be accessed on [web address].

Data will be entered directly on the THESEUS data collection portal, a web-based system designed specifically for the capture of data in THESEUS. Participants and clinicians will log on to the portal using a unique username and password, allocated to them by the Trial Manager or Data Manager. Data can be entered using a PC/laptop/smartphone. The data collection portal will be built with the ability to engineer printable version of the data collection forms if they are required. Data collected on paper will be added to the portal as required. Data collected on paper forms will be subject to a QC check against the data added to the portal for quality purposes as per the THESEUS data management plan. Further information pertaining to the management of study data can be found in the THESEUS data management plan.

17.2.2 Paper CRFs

In the event of the requirement for paper CRF's the top copy of each completed CRF should be returned to the CTR for data entry within four weeks of the visit. The remaining copy is to be retained at the local site within the Investigator Site File. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

CRF pages and data received by the CTR from participating study sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to respond to the data query on the data clarification form. The case report form pages should not be altered.

All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the CTR and a copy retained at the site along with the participants' CRFs.

The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

Further detail can be found in the THESEUS data management plan.

18 Protocol/GCP non-compliance

The Principal Investigator will report any non-compliance to the study protocol or the conditions and principles of Good Clinical Practice (GCP) to the CTR in writing as soon as they become aware of it.

19 End of study definition

The initial 6 months' treatment phase will be followed by a 6 months' follow-up period during which participants may switch from the intervention that was initially chosen.

The end of the study is defined as the date of final data capture to meet the study endpoints. In this case end of study is defined as 12 months' after enrolment of the final participant.

Sponsor must notify the main REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

20 Archiving

The Study Master File (SMF) and Study Site File (SSF) containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the SMF and SSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the study shall not be destroyed without permission from the Sponsor.

21 Regulatory Considerations

21.1 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This study protocol will be submitted through the relevant permission system for global governance review by Health and Care Research Wales Research Permissions.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

21.2 Data Protection

Confidentiality of study data will be ensured. Participants will always be identified using only their unique study identification number and any additional identifiers.

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016/679. The data controller and data processor for this study is Cardiff University (Sponsor).

21.3 Indemnity

Non-negligent harm: This study is an academic, investigator-led and designed study, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical study and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this study. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Study (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

21.4 Study sponsorship

Cardiff University will act as Sponsor for the study. Delegated responsibilities will be assigned to the sites taking part in this study and will be documented in the site agreement.

The Sponsor has/will be delegating certain responsibilities to Cardiff University's CTR (detailed in a Memorandum of Understanding), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

21.5 Funding

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 17/98/01), from a commissioned call regarding "Management of Hidradenitis Suppurativa" and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

The study is adopted on the NIHR portfolio.

Participant incentives of £20 will be offered at the end of the 12 months' follow up period in the cohort study and a further £20 for patient participation in the interview component. Travel expenses will be paid to those participants who attend the consensus workshop.

22 Study management

The Centre for Trials Research at Cardiff University will manage the study. The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, principles of Good Clinical Practice, EU General Data Protection Regulation 2016/679 and CTR standard operating procedures. The study manager will be responsible for running the study and will be accountable to the Sponsor.

22.1 SMG (Study Management Group)

A THESEUS Study Management Group (SMG) will oversee study design; study centre recruitment and study conduct; study management; study logistics and cost management; study methods; statistical data analysis; and publication. The SMG will comprise the chief investigator (CI) and THESEUS grant co-applicants, including our patient representative. SMG members will be required to sign up to the remit and conditions as set out in the SMG Charter.

22.2 Study Steering Committee /Data Monitoring Committee (SS/DM-C)

As a non-randomised, prospective cohort study, THESEUS will have a joint Study Steering/Data Monitoring Committee (SS/DM-C) to provide overall study supervision. The role of the SS/DM-C will be to provide overall supervision of the study on behalf of the NIHR. In particular, the SS/DM-C will focus on progress of the study, adherence to the protocol, patient safety and consideration of new information. There will be four independent members: a chairperson experienced in the conduct of clinical studies, an academic, a biostatistician and a patient representative. The CI will attend all meetings, accompanied by the study manager and other SMG/study staff as appropriate. The Steering committee will meet prior to study commencement to review the protocol, roles, responsibilities, and timelines for meetings and agree the remit and conditions set out in the SS/DM-C Charter.

23 Quality Control and Assurance

23.1 Risk Assessment

A Study Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This study has been categorised as a low risk non-CTIMP study, where the level of risk is comparable to the risk of standard medical care. A copy of the study risk assessment may be requested from the Study Manager. No routine monitoring is planned, however triggered monitoring may be required if a site issue is identified.

23.2 Monitoring

The clinical study risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the THESEUS study; triggered on-site monitoring will be employed.

Investigators should agree to allow study related monitoring, including audits, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

23.3 Audits & inspections

The CI or PI organisations/institution(s) will permit study-related monitoring, audits, REC/ Institutional Review Board (IRB) review, providing direct access to source data / documents.

The study may be participant to inspection and audit by Cardiff University under their remit as Sponsor.

24 Publication policy

All publications and presentations relating to the study will be authorised by the Study Management Group.

Results from all studies (cohort, mixed methods and outcome validation studies) will be presented and discussed during the final consensus workshop. This information will be used to inform discussions over preferred study design and priority research questions.

Results from the study will be distilled into a plain language summary that will be written in collaboration with our patient partners. It will be hosted on the HS Trust website and disseminated further via links in social media posts, such as the HS Trust, relevant research networks and journal Twitter feeds.

We will set up a THESEUS study website that will provide information about the study, both during the project and hosting the plain language summary and other outputs afterwards. The website will be designed so that the information is accessible to all stakeholders.

25 Milestones

Month 1-6 = Study Set Up

Month 7-30 = Patient Recruitment and Follow Up.

Month 30-36 = Results and Analysis

Month 31-36 = Consensus workshop.

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