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Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS): a prospective cohort study

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Abstract

Background Hidradenitis suppurativa (HS) is a chronic, painful disease affecting flexures and other skin regions, producing nodules, abscesses and skin tunnels. Laser treatment targeting hair follicles and deroofing of skin tunnels are standard HS interventions in some countries but are rarely offered in the UK.

Objectives To describe current UK HS management pathways and influencing factors to inform the design of future randomized controlled trials (RCTs).

Methods THESEUS was a nonrandomized 12-month prospective cohort study set in 10 UK hospitals offering five interventions: oral doxycycline 200 mg daily; oral clindamycin and rifampicin both 300 mg twice daily for 10 weeks, extended for longer in some cases; laser treatment targeting hair follicles; deroofing; and conventional surgery. The primary outcome was the combination of clinician-assessed eligibility and participant hypothetical willingness to receive each intervention. The secondary outcomes were the proportion of participants selecting each intervention as their final treatment option; the proportion who switch treatments; treatment fidelity; and attrition rates. THESEUS was prospectively registered on the ISRCTN registry: ISRCTN69985145.

Results The recruitment target of 150 participants was met after 18 months, in July 2021, with two pauses due to the COVID-19 pandemic. Baseline demographics reflected the HS secondary care population: average age 36 years, 81% female, 20% non-White, 64% current or ex-smokers, 86% body mass index $\geq$ 25, 68% with moderate disease, 19% with severe disease and 13% with mild disease. Laser was the intervention with the highest proportion (69%) of participants eligible and willing to receive treatment, then deroofing (58%), conventional surgery (54%), clindamycin and rifampicin (44%), and doxycycline (37%). Laser was ranked first choice by the greatest proportion of participants (41%). Attrition rates were 11% and 17% after 3 and 6 months, respectively. Concordance with doxycycline was 52% after 3 months due to lack of efficacy, participant choice and adverse effects. Delays with procedural interventions were common, with only 43% and 26% of participants starting laser and deroofing, respectively, after 3 months. Uptake of conventional surgery was too small to characterize the intervention. Switching treatment was uncommon and there were no serious adverse events.

Conclusions THESEUS has established laser treatment and deroofing for HS in the UK and demonstrated their popularity with patients and clinicians for future RCTs.

What is already known about this topic?

- There is a relative lack of evidence for the efficacy, tolerance and patient acceptability of many of the commonly used treatments for hidradenitis suppurativa (HS).
- The HS Priority Setting Partnership highlighted a top-10 set of research priorities to take forward.
- Deroofing and laser treatment targeting the hair follicle are rarely performed for HS in the UK but feature in HS treatment guidelines in other parts of the world.

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What does this study add?

- THESEUS established laser and deroofing treatment protocols for HS in the UK.
- Favourable recruitment and attrition rates were established for future HS studies.
- Laser and deroofing had the highest rates of patient willingness and clinician-assessed eligibility to receive treatment compared with conventional surgery, oral clindamycin and rifampicin, or oral doxycycline.

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that can have a large impact on quality of life due to pain, discharge of pus and scarring.[1] It is characterized by nodules, abscesses and skin tunnels (also known as sinus tracts or fistulae), typically occurring in flexural sites such as the axilla and groin, as well as nonflexural sites.[2] If left untreated, disease severity can progress from intermittent inflammatory lesions to multiple chronically inflamed scars. Management involves integration of medical therapy to reduce the inflammation and surgery to remove irreversible scarring.[3]

A Cochrane review of interventions for HS found that there were relatively few HS randomized controlled trials (RCTs) to guide patient care.[4] Since then, the pharmaceutical industry has initiated several RCTs investigating biologic therapies for HS; however, biologic therapy is relatively expensive and is currently located towards the end of the HS treatment pathway.[5,6] There is less trial activity involving surgery, laser and medical therapies such as antibiotics that are routinely used in HS but for which the evidence base remains relatively limited.

The design of the Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS) was influenced by several factors. Firstly, a James Lind Alliance-supported Priority Setting Partnership for HS identified and prioritized a top-10 list of HS research uncertainties.[7] Several of the uncertainties were incorporated into THESEUS, including the following: 'What is the most effective and safe group of oral treatments in treating HS (ranked number one priority)? What is the impact of HS and the treatments on people with HS (ranked third)? and What is the best surgical procedure to perform in treating HS (ranked sixth)?'.

Secondly, the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) funding body issued a call for studies to investigate 'What are the best management options for hidradenitis suppurativa when first line treatments fail?' The funding brief recommended a cohort study to lay the groundwork for future publicly funded RCTs.

Thirdly, THESEUS was designed to introduce laser treatment and deroofing as HS interventions into the UK. Several RCTs comparing the left and right sides of an affected skin region provide evidence for laser treatment targeting the hair follicle,[8,9] and appropriate laser services are available in the UK. However, prior to THESEUS, laser was very rarely used for HS therapy, in part due to funding issues, despite its potential role to treat active lesions and to prevent further lesions. Deroofing is a procedure usually performed under local anaesthetic which involves blunt probing of skin tunnels to identify all the branches and then removing the roof to allow the base to heal by secondary intention.[10] It is a tissue-conserving procedure that reduces healing times compared with wide excision and can be performed by dermatologists and surgeons straightforwardly in a procedure room, but was not being performed in the UK prior to THESEUS despite being included in the European HS treatment guidelines.[6]

In planning THESEUS, surveys were sent to dermatologists,[11] surgeons[12] and general practitioners[13] to confirm HS treatments and pathways of care in use in the UK at the time. The surveys demonstrated considerable variation in HS care likely to result in inequality of access to treatment and poorer outcomes for some UK residents with HS depending on their geographical location.

The objectives of the prospective cohort component of THESEUS were to: (i) understand current HS patient pathways and what influences treatment choices to inform the design of future RCTs; (ii) determine the feasibility of recruiting individuals with HS into UK clinical trials; and (iii) fully characterize the THESEUS drug and procedural interventions. Additional objectives to test the feasibility and responsiveness of outcome measure instruments (OMIs) for HS trials and explore consensus-agreed recommendations for future RCT study designs are covered in other publications (Hasan *et al.*, paper submitted).[14]

Materials and methods

Study design

The full protocol for THESEUS has been published[15] and the study was prospectively registered on 9 August 2019 in the ISRCTN Registry (reference: ISRCTN69985145). THESEUS was a UK multicentre prospective nonrandomized observational cohort study. The following five interventions were offered: (i) oral doxycycline 200 mg once daily; (ii) oral clindamycin and rifampicin, both 300 mg twice daily for 10 weeks initially; (iii) laser treatment targeting the hair follicle (Nd: YAG, diode or alexandrite); (iv) deroofing; and (v) conventional surgery with the procedure and closure method determined by the operating surgeon.

Recruitment was achieved via a network of 10 hospitals spread across the UK, six sites being dermatology-led and two plastic surgery-led, with two already having a HS multidisciplinary team approach integrating medical and surgical HS care. The sites were required to offer at least four of the five THESEUS interventions and were purposively selected to help balance recruitment into each intervention arm.

In this nonrandomized study, the final intervention choice was based on participant preference for each of the interventions, combined with clinician-assessed eligibility, the shared decision-making process designed to replicate regular clinical practice. Participant preference was supported by a decision grid which described each intervention and provided the potential benefits and adverse effects in a head-to-head

comparison (Table S1; see Supporting Information). A video was also produced giving participants details of the deroofing intervention procedure (https://www.youtube.com/watch?v=ftizgrBMzok&t=190s).[16] Participants were asked to remain on their chosen intervention for the first 6 months, unless another treatment was medically indicated, after which they could switch intervention if they wished.

Except for the final few recruits, 12 months of follow-up was undertaken, with study visits every 3 months, mirroring routine care. Participant demographics and previous HS medical and surgical treatment were recorded at baseline. Clinical examination at each review established the Hurley and refined Hurley stage defining baseline mild, moderate and severe disease,[17] and lesion counts were performed to demonstrate changes in disease severity via the International Hidradenitis Suppurativa Severity Score System (IHS4) instrument[18] and Hidradenitis Suppurativa Clinical Response (HiSCR) trial endpoint.[19] Questionnaires were also administered to measure all six of the core domains recommended by the HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC).[20] These included pain numerical rating scale (NRS), HS quality of life questionnaire (HiSQOL),[21] Patient Global Assessment,[22] number of patient-reported HS flares, the use of dressings, and fatigue.[23] Dermatology Life Quality Index (DLQI)[24] and general health-related quality of life (EQ-5D-5L) questionnaires were also administered. In addition, a text message was sent to consenting participants every day for 12 weeks, beginning on the day the intervention commenced, to prompt a response recording pain NRS.

As a pragmatic study, inclusion and exclusion criteria were designed to allow most patients with HS in secondary care to participate if they wished. Inclusion criteria were: (i) HS defined as a lifetime history of at least five flexural skin boils or two in the last 6 months, confirmed on examination by a clinician with HS experience; (ii) at least 18 years old with active HS despite current treatment; and (iii) any stage of disease severity provided at least one of the THESEUS

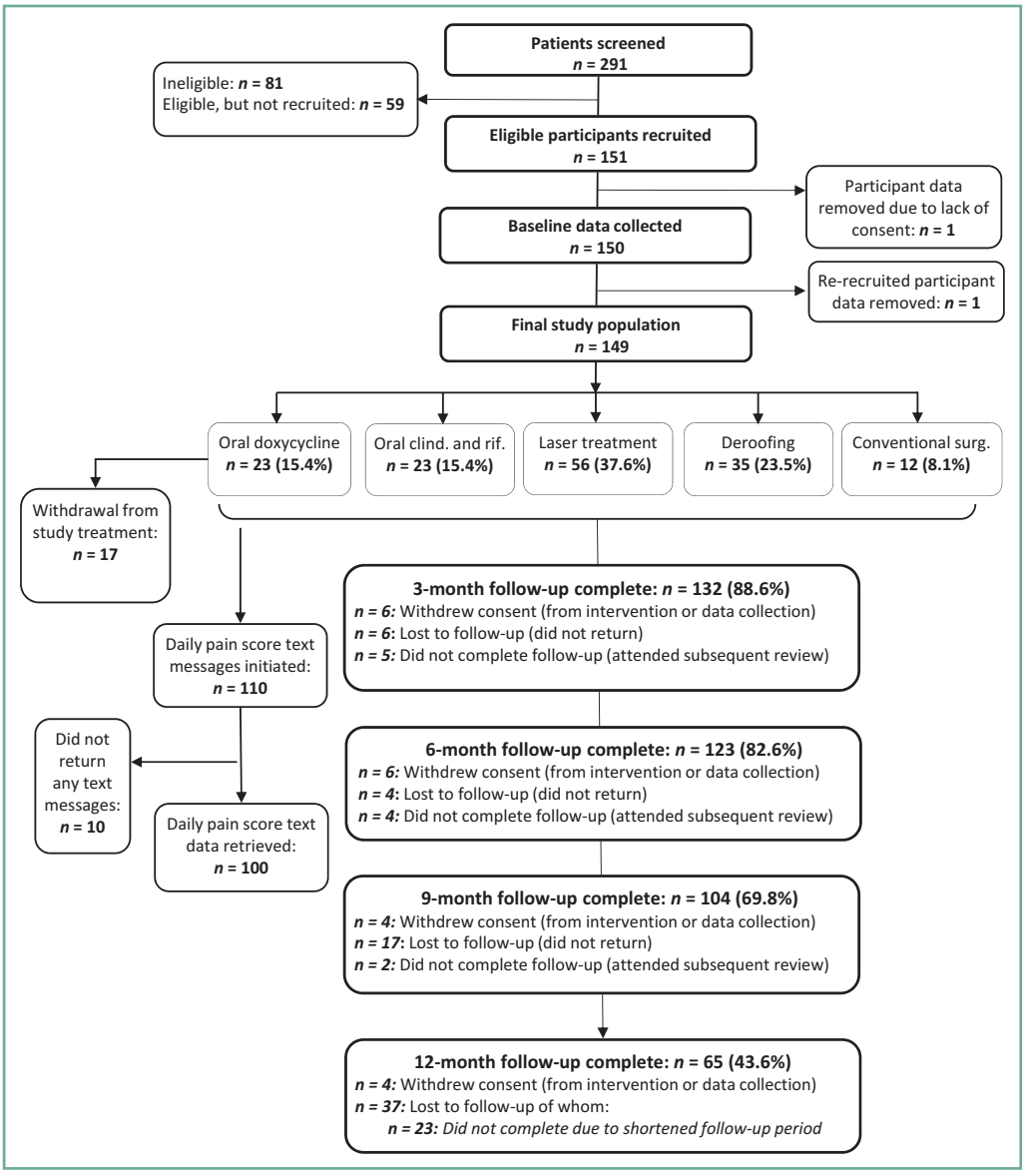

Figure 1 Flow diagram of screening, recruitment and participant attrition.Oral clind. and rif., Oral clindamycin and rifampicin.

interventions was suitable. Exclusion criteria were: (i) unable or unwilling to provide written informed consent; (ii) pregnant or breast feeding; and (iii) unable to complete outcome questionnaires in English. Participants could continue their current medical treatment on entry to the study, provided it was compatible with their chosen THESEUS intervention. Laser therapy was avoided in those taking oral tetracyclines due to the potential for photosensitivity. There were no restrictions on analgesia during the study.

Primary and secondary outcomes

The primary outcome of THESEUS was the proportion of participants who were eligible and hypothetically willing to receive the study interventions. Secondary outcomes were: (i) proportion selecting each intervention as their final choice with underpinning reasons; (ii) proportion of participants switching treatments, with reasons; (iii) treatment fidelity (concordance); (iv) loss to follow-up over 12 months; and (v) determination of OMI responsiveness based on outcomes after 6 months.

In keeping with an observational study, investigators recorded any adverse effects of THESEUS interventions at the time of scheduled follow-up visits. Usual processes were followed for managing adverse effects, including UK yellow card reporting if needed. Characterization of procedures was achieved by operators completing a report form in each case.

Sample size and statistical analysis

The reporting of this study is in accordance with STROBE guidelines (Table S2; see Supporting Information). The required sample size was 150 participants, allowing the proportion of participants hypothetically willing and eligible to be randomized in a clinical study to be estimated within a 95% confidence interval of ±7%. The pre-study surveys confirmed that the sample size should ensure recruitment of at least 20 participants for each intervention, sufficient to explore delivery in an IDEAL 2b evaluation, which provides a framework for the introduction of a novel surgical intervention.[25] THESEUS was not powered to test the relative efficacy of interventions and in most cases the analysis was limited to descriptive statistics (frequencies and percentages, mean and SD, median and interquartile range). Statistical analysis was performed in Stata, v.17, 2021 (StataCorp LLC Stata Statistical Software, College Station, TX, USA). The analysis was based on the participants' final treatment selection.

Patient and public involvement

Patient research partners (PRPs) were integral to the design and delivery of THESEUS. Three leaders of the HS Trust patient advocacy organization were members of the Study Management Group and Study Steering Committee. THESEUS PRPs recommended the creation of the decision grid (Table S1) and selected the timing of the daily text messages at 6 pm, with responses up to 2 am being valid. Our PRPs also advised on COVID-19 pandemic mitigation strategies, including flexible remote follow-up where necessary.

Results

Participant recruitment commenced in February 2020 and the target of 150 participants was reached in July 2021 (see Figure 1 for the CONSORT study flow diagram). There were two pauses in recruitment reflecting the two waves of the COVID-19 pandemic in the UK in the Spring and Winter of 2020 (Figure 2). Overall, 291 patients were screened, of

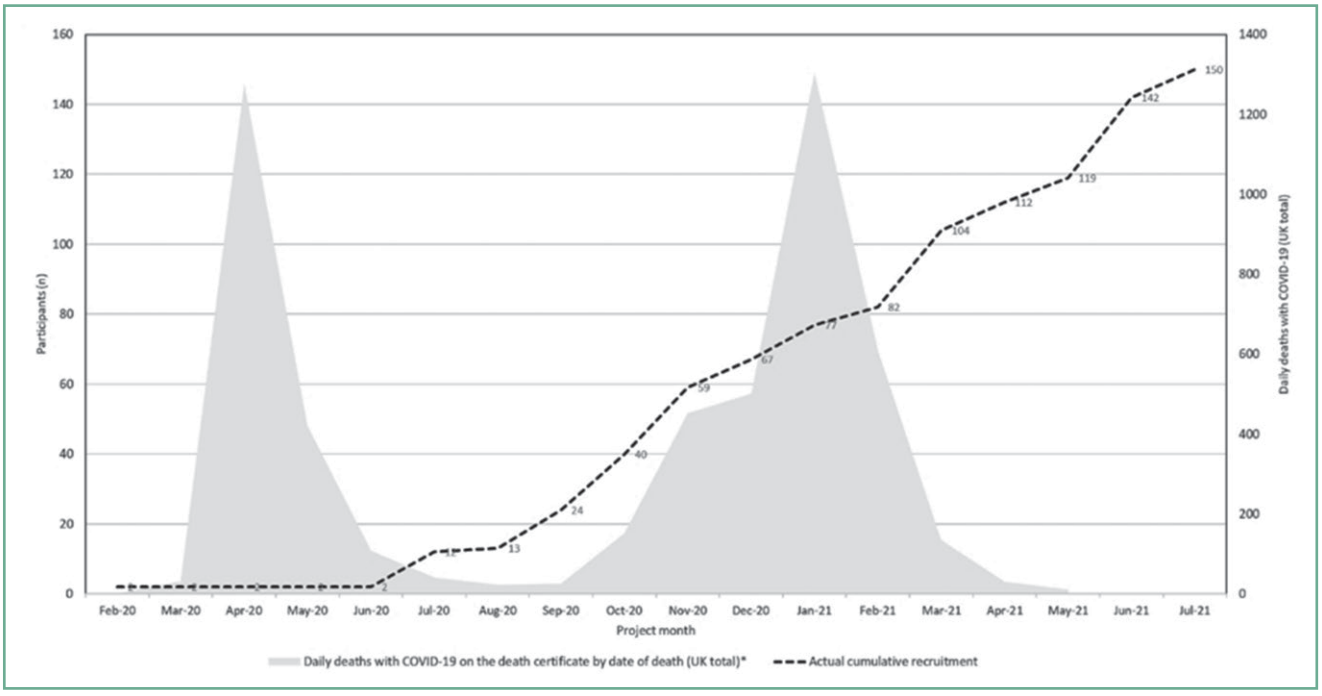

Figure 2 Cumulative recruitment influenced by COVID-19 pandemic.

whom 149 (51%) were recruited; reasons for ineligibility and those who were eligible but declined are shown in Table S3 (see Supporting Information). The follow-up rates were 89% ($n=132$), 83% ($n=123$), 70% ($n=104$) and 44% ($n=65$) at 3, 6, 9 and 12 months, respectively (Figure 1). The 12-month follow-up rate was affected by pandemic-induced recruitment delays, which prevented 23 participants reaching the final follow-up before THESEUS was closed to adhere to pre-specified study timelines. There were 17 study withdrawals, two from the doxycycline arm, three from clindamycin and rifampicin, eight from laser, one from deroofing and three from conventional surgery.

The baseline demographics of the study participants are shown in Table 1. The average age was 36 years (SD 10.5), 81% ($n=121$) were female, 20% ($n=30$) had non-White ethnicity, 86% had an elevated body mass index (≥ 25.0) and 64% ($n=95$) were current or ex-smokers. Just over two-thirds of participants (69%, $n=102$) were Hurley stage II (moderate) at baseline, 19% ($n=28$) were stage III (severe) and 13% ($n=19$) were stage I (mild) (Table 2). Recent interventions received prior to study entry are shown in Table S4 (see Supporting Information): 26% of participants received oral tetracyclines in the previous month and only 6% received adalimumab in the previous 3 months. Two-thirds (65%, $n=95$) of participants had received recent care from a dermatologist, 31% ($n=45$) from a surgeon and 20% ($n=29$) from the Accident and Emergency Department (Table 2).

Laser was the most popular intervention from a participant's perspective, with 40% ($n=52$) ranking it their most preferred option (Table 3). The THESEUS primary outcome of participant willingness and clinician-assessed eligibility to receive treatment was highest for laser (69%, $n=102$), followed by deroofing (58%, $n=86$), conventional surgery (54%, $n=80$), clindamycin and rifampicin (44%, $n=65$) and then doxycycline (37%, $n=55$) (Table 4) and this was mirrored by final intervention choice (Table 5).

Characterization of ineligibility to receive the THESEUS interventions demonstrated that those with migratory skin lesions and absence of skin tunnels were less suited to deroofing or conventional surgery (Table S5; see Supporting Information). Participants with mild disease were more

Table 1 Baseline characteristics of participants (overall, $n=149$)

Demographics	Descriptive statistics
Age (years), mean (SD)	36.1 (10.5)
Female, *n* (%)	121 (81.2)
Ethnic group or background ($n=148$), *n* (%)	
White	118 (79.7)
Mixed/Multiple ethnic groups	8 (5.4)
Asian/Asian British	9 (6.1)
Black/African/Caribbean/Black British	11 (7.4)
Other ethnic background	2 (1.4)
Fitzpatrick scale ($n=148$), *n* (%)	
I: Very fair; always burns, cannot tan	17 (11.5)
II: Fair; usually burns, sometimes tans	50 (33.8)
III: Medium; sometimes burns, usually tans	46 (31.1)
IV: Olive; rarely burns, always tans	13 (8.8)
V: Brown; rarely burns, tans easily	16 (10.8)
VI: Dark brown; never burns, always tans	6 (4.1)
Body mass index (BMI), $n=143$ (kg m^{-2})	
BMI, mean (SD)	33.0 (7.9)
Healthy weight (BMI $\geq$ 18.5 to 24.9 kg m^{-2}), *n* (%)	20 (14.0)
Overweight (BMI $\geq$ 25.0 to 29.9 kg m^{-2}), *n* (%)	40 (28.0)
Obese (BMI $\geq$ 30.0 to 39.9 kg m^{-2}), *n* (%)	54 (37.8)
Severely obese (BMI $\geq$ 40 kg m^{-2}), *n* (%)	29 (20.3)
Index of Multiple Deprivation quintiles,[a] *n* (%)	
1: Most deprived	37 (24.8)
2	37 (24.8)
3	31 (20.8)
4	29 (19.5)
5: Least deprived	15 (10.1)
Type of study site, *n* (%)	
Dermatology-led (6 sites)	64 (43.0)
Surgery-led (2 sites)	50 (33.5)
Pre-established multidisciplinary service (2 sites)	35 (23.5)
Smoking ($n=148$), *n* (%)	
Nonsmoker	53 (35.8)
Ex-smoker	32 (21.6)
Current smoker	63 (42.6)
For smokers, number cigarettes smoked per day, median (IQR)	10.0 (5.0–11.0)
Nicotine replacement therapy ($n=147$), *n* (%)	21 (14.3)

IQR, interquartile range. [a]Index of Multiple Deprivation is a standard dataset used in the UK to classify the relative affluence or poverty of small geographical areas.

Table 2 Baseline hidradenitis suppurativa (HS) severity and specialty providing HS care (overall, $n=149$)

Baseline variables	Descriptive statistics
Clinical history	
Participants' HS recently treated by ($n=147$), *n* (%)	
General practitioner	103 (70.1)
Dermatologist	95 (64.6)
Surgeon	45 (30.6)
Doctor in Accident and Emergency	29 (19.7)
Nurse (community/primary care)	29 (19.7)
Anybody else (others)	12 (8.1)
Qualities of HS	
Skin region affected, *n* (%)	
Axilla	102 (68.5)
Groin	114 (76.5)
Perineum	47 (31.8)
Buttocks	58 (38.9)
Chest	46 (30.9)
Other	45 (30.4)
Total number of inflammatory nodules, median (IQR)	4 (1.0–8.5)
Total number of abscesses, median (IQR)	1 (0–3)
Total number of draining or inflamed skin tunnels, median (IQR)	1 (0–2)
IHS4,[a] median (IQR)	11 (4–21)
Number of HS flares in the last month, median (IQR)	4 (2–10)
Drainage of pus, blood, other fluid due to HS,[b] median (IQR)	3.5 (0–6)
Magnitude of skin odour,[b] median (IQR)	3.5 (0–7)
Hurley stage (most severely affected region), *n* (%)	
I: Mild: individual, nonscarring lesions	19 (12.8)
II: Moderate: multiple scarring lesions separated by normal skin	102 (68.5)
III: Severe: lesions coalescing into inflammatory plaques	28 (18.8)
Skin lesions fixed in location or migratory ($n=148$), *n* (%)	
Fixed	94 (63.5)
Migratory	54 (36.5)
Draining skin tunnels due to HS present in any skin region ($n=148$), *n* (%)	86 (58.1)
Three or more body regions with draining skin tunnels, *n* (%)	27 (18.1)
Skin regions across body with at least 1% interconnected draining tunnels, *n* (%)	15 (10.1)
Refined Hurley stage for HS severity, *n* (%)	
Hurley IA	13 (8.7)
Hurley IB	32 (21.5)
Hurley IC	18 (12.1)
Hurley IIA	12 (8.1)
Hurley IIB	14 (9.4)
Hurley IIC	45 (30.2)
Hurley III	15 (10.1)
How was lesion count assessed for the purposes of this review ($n=68$), *n* (%)[c]	
In person, by a health professional	47 (69.1)
Self-reported, by the patient	21 (30.9)

IHS4, International Hidradenitis Suppurativa Severity Score System; IQR, interquartile range. [a]IHS4 score is calculated by the number of inflammatory nodules plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4); higher score indicates more severe disease. [b]Scored from 0 to 10 where 0 is none and 10 is worst imaginable. [c]Question was added when remote lesion count assessment was permitted midway through recruitment.

willing to receive the antibiotic interventions, while those with moderate-to-severe disease favoured nonantibiotic options (Table S6; see Supporting Information). Participant-reported reasons for final intervention choice were dominated by 'My doctor recommended it', followed by 'I wanted to try something new' (Table 5), as confirmed by a nested qualitative interview study (Howells *et al.*, paper submitted).

Treatment concordance is summarized in Tables S7–S11 (see Supporting Information). Of the 23 participants who chose doxycycline, concordance (in receipt of treatment) was 52% ($n=12$) after 3 months, and then 57% ($n=13$), 26% ($n=6$) and 17% ($n=4$) after 6, 9 and 12 months, respectively. Concordance with clindamycin and rifampicin was lower (30%, $n=7$ of 23) at 3 months, as participants were likely to have completed the initial 10-week course of treatment. Fidelity for the nonantibiotic interventions was substantially affected by delays in commencing treatment, due to a combination of THESEUS not mandating the timing of treatment as a nonrandomized observational study, compounded by pandemic-induced delays. Only 43% ($n=24$) of the 56 participants choosing laser and one-quarter ($n=9$) of the 35 participants selecting deroofing had started treatment at the 3-month review.

Efficacy data for each intervention during the 12 months of follow-up are presented in Table S12 (see Supporting Information). In the doxycycline arm after 3 months there were modest reductions in HS severity (IHS4 score from 7 to 6), health-related quality of life (HiSQOL score from 26.5 to 11.5 points, DLQI score from 6 to 3.5) and pain (pain NRS from 2 to 1). The small effect size may reflect relatively low

Table 3 Participant willingness and clinician-assessed eligibility for THESEUS interventions ($n = 149$)

	Doxycycline	Clindamycin and rifampicin	Laser	Deroofing	Conventional surgery
			n (%)		
Willingness					
Participant willing to receive treatment	63 (42.3)	76 (51.0)	118 (79.2)	99 (66.4)	95 (63.8)
Unwillingness, reasons for					
Will not provide enough benefit	14 (9.4)	12 (8.1)	18 (12.1)	23 (15.4)	19 (12.8)
Potential side-effects/complications	11 (7.4)	12 (8.1)	1 (0.7)	5 (3.4)	13 (8.8)
Had this before: not effective	40 (26.8)	29 (19.5)	1 (0.7)	4 (2.7)	3 (2.0)
Had this before: experienced side-effects	15 (10.1)	14 (9.4)	1 (0.7)	0 (0.0)	0 (0.0)
Information from other sources	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	2 (1.3)
Other reason	6 (4.0)	6 (4.0)	9 (6.0)	17 (11.4)	16 (10.7)
Patient ranked 1 (most preferred)	17 (13.2)	19 (14.7)	52 (40.3)	26 (20.2)	15 (11.6)
Clinician-assessed eligibility					
Clinically appropriate	88 (59.5)	96 (64.4)	89 (59.7)	100 (67.1)	94 (63.1)
Eligible but treatment not available at the site	NA	NA	22 (14.8)	NA	NA

NA, not applicable.

baseline disease severity in this group. In the clindamycin and rifampicin arm, score reductions after 3 months were from 11 to 5 points for IHS4, 34 to 23 points for HiSQOL, 14 to 10.5 for DLQI and from 4 to 2 for pain NRS. Interpretation of efficacy data for the nonantibiotic interventions is limited by the variable timing of intervention delivery across the 12 months of follow-up. There were no serious adverse events and a total of 37 adverse effects were recorded from 29 participants (Table S13; see Supporting Information), the commonest being gastrointestinal effects of the antibiotic interventions which led to treatment discontinuation in eight participants in the doxycycline arm (35%) and nine participants on rifampicin and clindamycin (39%). Laser and deroofing were both well-tolerated interventions.

In characterizing the laser intervention, there were 196 procedures involving 56 participants. Four initial treatments 1 month apart were recommended and this was reflected by four being the mode of the number of treatments received (Figure 3), with a range from one to nine. Alexandrite was the commonest laser modality (44%), followed by Nd:YAG (14%). In addition, 36% were intense pulsed light (IPL) treatment, which was not specified in the study protocol.[15] A total of 41 deroofing procedures were performed for 30 participants, 49% in the axilla and 32% in the groin. There was variation in the instrument used for incision, with needle-tip diathermy used more often than loop diathermy. Identification of skin tunnels by blunt probing and secondary-intention healing of the wound were highly conserved and performed for nearly all procedures. Low uptake of conventional surgery, due to lower participant preference and pandemic-related delays, meant there were insufficient procedures to characterize this intervention.

Table 4 Primary outcome: participant willingness and eligibility for THESEUS interventions

Primary outcome: patients willing and eligible for study intervention[a]	***n* (%)**
Doxycycline	55 (36.9)
Clindamycin and rifampicin	65 (43.6)
Laser	102 (68.5)
Deroofing	86 (57.7)
Conventional surgery	80 (53.7)

[a]Patients could be willing and eligible for more than one treatment; categories are not mutually exclusive.

Discussion

THESEUS was a nonrandomized, prospective observational cohort study designed to lay the foundations for future RCTs for HS. A spectrum of five interventions – medical, laser and surgical – in addition to the relatively broad eligibility criteria, ensured THESEUS was as inclusive as possible, reflected by recruitment of 51% of secondary care patients screened. The study successfully introduced laser treatment targeting the hair follicle and deroofing to the UK, which previously were rarely offered, providing training and equipment for 10 centres spread across the country. The upskilled centres are well placed to act as training hubs for their regions and to participate in future HS trials involving laser or deroofing.

Participant willingness and clinician-assessed eligibility for each intervention, the primary outcome of THESEUS, was greatest for laser treatment (69% of participants), followed by deroofing (58%), conventional surgery (54%), combined oral clindamycin and rifampicin (44%) and then oral doxycycline (37%). Final intervention choice was lower for conventional surgery than might be expected, probably reflecting the popularity of deroofing and pandemic-associated delays linked to reduced operating theatre access for surgical procedures requiring a general anaesthetic. Support for deroofing as an intervention is further indicated by the THESEUS deroofing information video (https://www.youtube.com/watch?v=ftizgrBMzok&t=190s)[16] receiving more than one million views so far.

Doxycycline and other tetracyclines remain standard first-line oral therapy for HS and could be a comparator arm in future RCTs, while being mindful of the relatively high treatment discontinuation rate in THESEUS. It should be noted that RCT evidence is currently limited to a single small trial comparing oral tetracycline with topical clindamycin from more than 20 years ago, using OMIs that have now been superseded.[26] THESEUS used doxycycline 200 mg daily, twice the standard dose for acne and in line with treatment for other

Table 5 Final intervention choice and participant reported reasons

	Final intervention choice,[a] *n* (%)				
	Doxycycline	**Clindamycin and rifampicin**	**Laser**	**Deroofing**	**Conventional surgery**
	23 (15.4)	23 (15.4)	56 (37.6)	35 (23.5)	12 (8.1)
Patients' ranking of treatment					
1: most preferred	16 (70)	19 (83)	51 (91)	25 (71)	11 (92)
2			1 (2)	1 (3)	
3	1 (4)			1 (3)	
4	1 (4)	3 (13)			
5: least preferred					
Missing	5 (22)	1 (4)	4 (7)	8 (23)	1 (8)
Reason for deciding on the final treatment:[b]					
My doctor recommended it	15 (65.2)	15 (68.2)	27 (49.1)	27 (77.1)	3 (25.0)
I wanted to try something new	5 (21.7)	5 (22.7)	15 (27.3)	2 (5.7)	1 (8.3)
I've used it before	1 (4.3)	1 (4.5)	0	0	4 (33.3)
Based on:[b]					
Information read in THESEUS information sheet	2 (8.7)	0	5 (9.1)	2 (5.7)	0
Information read on website(s)	0	0	1 (1.8)	1 (2.9)	2 (16.7)
Information read in THESEUS decision grid	0	1 (4.5)	1 (1.8)	0	0
My preferred option was not available	0	0	1 (1.8)	1 (2.9)	0
Other reason[b]	0	0	5 (9.1)	2 (5.7)	2 (16.7)

[a]Patients could choose only one intervention as their final choice; [b]two missing values: clindamycin and rifampicin, $n=22$; laser, $n=55$.

inflammatory skin conditions.[27] Combined oral clindamycin and rifampicin is a standard treatment recommended by several HS guidelines,[5,6,28] while lacking RCT evidence. Another prospective cohort study of 103 participants found similar results to THESEUS, with a reduction in median IHS4 score from 13 to 6, and a treatment discontinuation rate due to adverse effects of 16%, compared with 22% in THESEUS.[29]

Strengths of THESEUS include the 12 months of follow-up, providing prospective data that are greatly needed in HS. Disease progression was relatively static during follow-up, with the proportion of participants with Hurley stage III severe disease stable at 19%, 16% and 21% across the baseline, 6-month and 12-month reviews, respectively (see Table S12). The baseline demographics of THESEUS participants, including two-thirds having moderate disease at baseline, are aligned with other studies[30] and THESEUS included proportionately slightly more non-White participants than in the overall UK population.

Limitations of THESEUS include unexpected variation in the laser intervention, with one-third of the procedures using IPL instead of laser. Nevertheless, several trials have found benefit in using IPL in HS,[31] and the mechanism of action, targeting the hair follicle, is very similar. Inclusion of IPL as well as laser treatment targeting the hair follicle in future RCTs for HS will depend on access to each modality and whether the

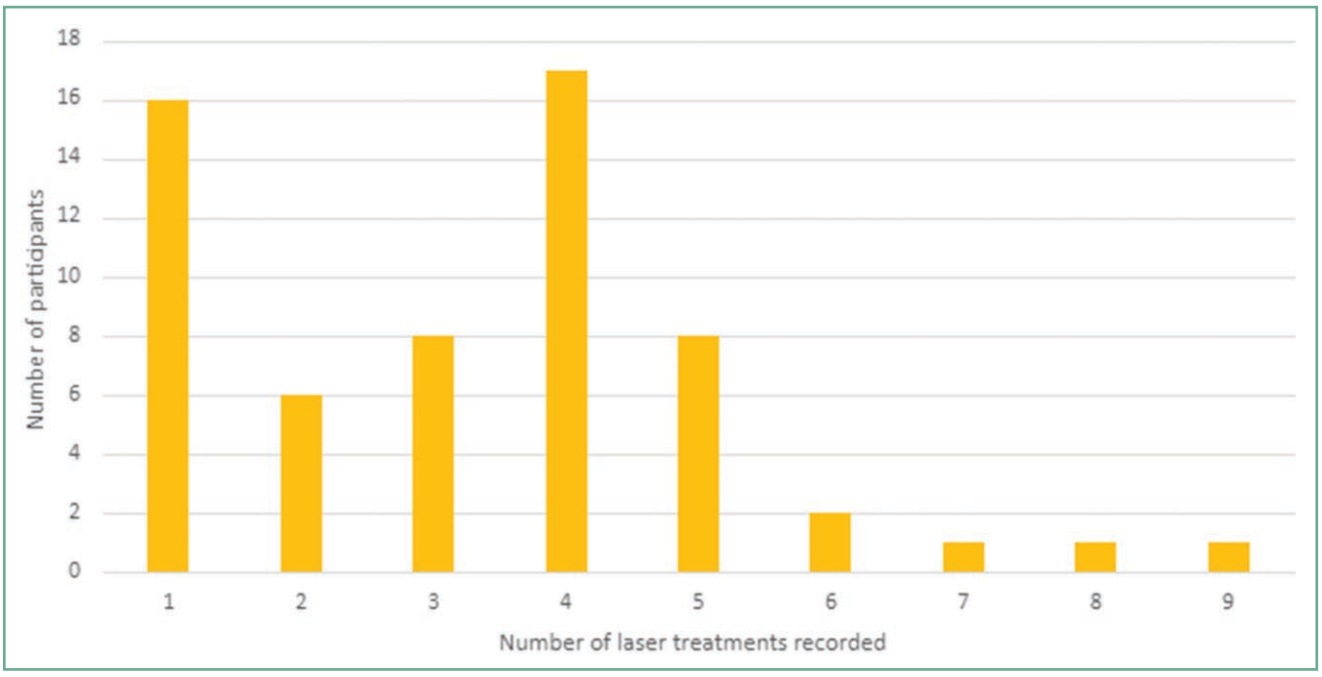

Figure 3 Number of laser/light treatments per participant.

trial is located towards the pragmatic or explanatory ends of the RCT spectrum. Delays encountered in the provision of nonmedical interventions mean that interpretation of efficacy data is limited; however, THESEUS was not powered to provide robust comparative effectiveness results. Another limitation is that only one treatment video was produced, which could have made deroofing more popular; however, some participants chose not to receive deroofing after viewing the video. In addition, while retention rates were quite high for the first 6 months of the study, attrition was a factor at the 9- and 12-month assessment points.

In conclusion, participant willingness and clinician-assessed eligibility for the five THESEUS interventions were greatest for laser and deroofing and THESEUS has introduced both interventions for HS to the UK. Further THESEUS details are provided in the HTA funding report (Ingram *et al.*, paper submitted) and in publications covering results from a nested process evaluation including participant interviews (Howells *et al.*, paper submitted), the feasibility of collecting daily pain NRS scores via text message (Hasan *et al.*, paper submitted), and the outcomes from the THESEUS end-of-study workshop proposing future RCT designs.[14]

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Conflicts of interest

J.R.I. receives a stipend as Editor-in-Chief of the *British Journal of Dermatology* and an authorship honorarium from UpToDate. He is a consultant for AbbVie, Boehringer Ingelheim, ChemoCentryx, Citryll, MoonLake, Novartis and UCB Pharma and has served on advisory boards for Insmed, Kymera Therapeutics and Viela Bio. He is co-copyright holder of HiSQOL, Investigator Global Assessment and Patient Global Assessment instruments for hidradenitis suppurativa (HS). His department receives income from the copyright of the Dermatology Life Quality Instrument (DLQI) and related instruments. R.C.-J. was a UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Associate Board Member (May 2018 to March 2020). F.C. is a consultant for UCB Pharma and received a fee from Daylong for participating in a HS consensus meeting. L.H. has received consultancy fees from the University of Oxford for an educational grant funded by Pfizer, unrelated to the submitted work. K.H. is a member of the NIHR HTA General Committee (2016–2022), the NIHR HTA Funding Committee Policy Group (2017–2022) and the NIHR Research Professors Panel (2019–present).

Data availability

All data requests should be submitted for consideration to: ctrdatasamplerequests@cardiff.ac.uk. Access to anonymized data may be granted following review.

Ethics statement

The Wales Research Ethics Committee 4 provided ethical approval for THESEUS on 26 September 2019, reference number 19/WA/0263.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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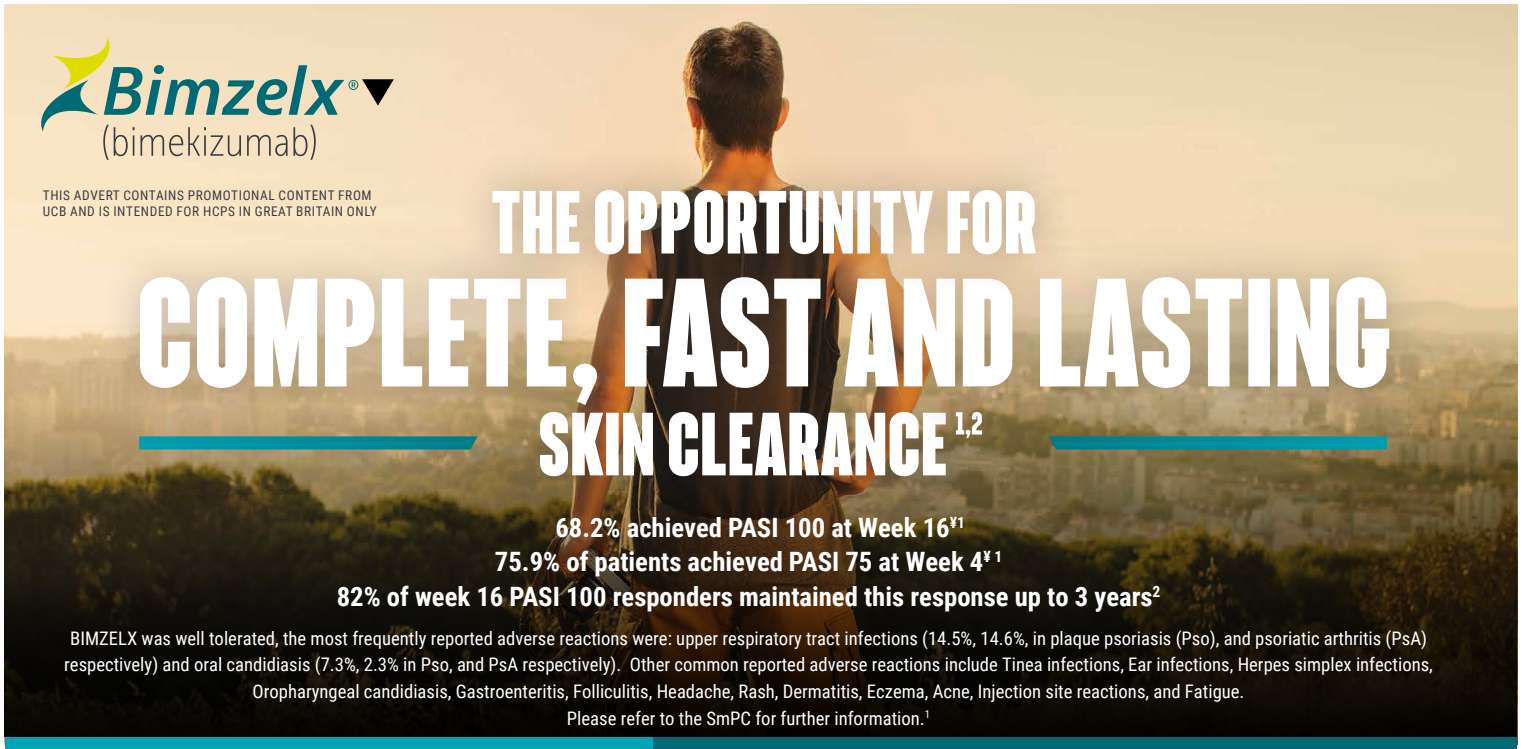

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Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy. **Dosage and Administration:** Should be initiated and supervised by a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated. **Recommended dose:** Plaque Psoriasis: 320 mg (given as two subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. Psoriatic arthritis: 160 mg (given as 1 subcutaneous injection of 160 mg) every 4 weeks. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the recommended dose is the same as for plaque psoriasis. After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160 mg every 4 weeks can be considered. Axial spondyloarthritis (nr-axSpA and AS): 160 mg (given as 1 subcutaneous injection) every 4 weeks. 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