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SIGNET: protocol for a multicentre, single-blind prospective, group sequential, randomised controlled trial to evaluate the benefits of a single dose of simvastatin given to potential organ donors declared dead by neurological criteria on outcomes in organ recipients

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ABSTRACT

Introduction Successful organ transplantation in patients with end-stage organ failure improves long-term survival, improves quality of life and reduces costs to the NHS. Despite an increase in the number of deceased organ donors over the last decade, there remains a considerable shortfall of suitable organs available for transplantation. Over half of UK donors are certified dead by neurological criteria following brain stem compression, which leads to severe physiological stress in the donor, combined with a hyperinflammatory state. Brain stem death-related dysfunction is an important reason for poor organ function and hence utilisation. For example, more than 30% of donation after brain stem death cardiac transplant recipients need short-term mechanical cardiac support, reflecting donor heart dysfunction.

A small, randomised study previously showed improved outcomes for cardiac transplant recipients if the donor was given simvastatin. SIGNET takes inspiration from that study and hypothesises a potential reduction in damage to the heart and other organs during the period after diagnosis of death and prior to organ retrieval in donors that receive simvastatin.

Methods and analysis SIGNET is a multicentre, single-blind, prospective, group sequential, randomised controlled trial to evaluate the benefits of a single high dose of simvastatin given to potential organ donors diagnosed dead by neurological criteria on outcomes in all organ recipients. The trial will run across a minimum of 89 UK sites with a recruitment target of 2600 donors over 4 years.

Ethics and dissemination SIGNET received a favourable opinion from the London, Queen Square Research Ethics Committee (Ref: 21/LO/0412) and following approval of substantial amendment 1 in January 2023, the current protocol is version 2 (7 December 2022). Substantial amendment 1 clarified consent procedures and added additional sites and prescribers. Findings from the study will be publicly available and disseminated locally and internationally through manuscript publications in peer-reviewed journals and conference presentations at national and international platforms.

Trial registration number ISRCTN11440354

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ SIGNET uses the UK's unique infrastructure for organ donation and transplantation (a network of specialist nurses for organ donation and data linkage to the UK Transplant Registry).
⇒ SIGNET is the first national UK organ donor intervention study and the methodology is likely to have applications beyond the trial intervention and setting.
⇒ At the end of recruitment, SIGNET will be the largest organ donor intervention trial in the world.
⇒ SIGNET will look at the effect of simvastatin on recipients of all organs transplanted from donors recruited to the study.
⇒ One limitation is that recipient outcomes are limited to those collected on the UK Transplant Registry.

ADMINISTRATIVE INFORMATION

The Newcastle upon Tyne Hospitals NHS Foundation Trust (tnu-tr.sponsormanagement@nhs.net) is the sponsor for SIGNET with responsibility to ensure that the study design meets regulatory standards with

arrangements in place for appropriate conduct and reporting (sponsor Ref. 9691).

Trial management of SIGNET has been delegated to NHS Blood and Transplant Clinical Trials Unit (NHSBT CTU) who, in conjunction with chief investigators and coapplicants, produced the protocol and associated study documents. NHSBT CTU oversees trial setup and ensures adherence to trial regulatory standards and safe running of the study aligned to the protocol across NHS Trusts. NHSBT CTU is also responsible for data management, quality assurance and safety monitoring.

The NHSBT CTU statistics team are responsible for the statistical analysis plan and will oversee the ongoing and final analysis of data.

Administration of contracts and finance is delegated to Newcastle University, holder of the study budget and responsible for reporting to the funder.

INTRODUCTION

Successful organ transplantation has substantial benefits for all recipients with dramatically improved survival, improved quality of life and reduced costs to the National Health Service (NHS). Median survival after cardiac transplantation is 12 years in the UK with excellent quality of life.[1 2] The health economic advantages are greatest for kidney transplantation, with annual savings twice the recommended National Institute for health and Care Excellence threshold for cost-effectiveness.[3]

Despite an increase in the number of deceased organ donors over the last decade, there remains a considerable shortfall of organs available for transplantation. The total number of transplants has been falling since 2017–2018 including a 10% reduction in the number of heart transplants.[4] Across all organs in 2022–2023, 439 patients died waiting and 732 were removed from the waiting list (ultimately leading to death).

Brain stem compression which very frequently leads to a diagnosis of death by neurological criteria also causes severe physiological stress in the donor, combined with a hyperinflammatory state.[5 6] Although thoracic organs offered by donation after brain stem death (DBD) donors are commonly turned down for transplantation due to pre-existing disease (65% of hearts and up to 85% of lungs), brain stem death-related organ dysfunction is an important reason for subsequent poor organ transplant utilisation. Even if organs are deemed transplantable, subsequent organ dysfunction causes morbidity and mortality in recipients, for example, more than 30% of DBD cardiac transplant recipients need short-term mechanical cardiac support, reflecting donor heart dysfunction. Almost all of the 18% mortality in the first year is in this group. It may be possible to prevent or mitigate the degree of organ impairment which occurs during the period of 'donor management' after the diagnosis of death.[7]

Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, an enzyme involved in cholesterol synthesis, especially in the liver. There is evidence that these medications also reduce inflammation in the body and in individual organs.[8] This suggests that statins have the potential to better preserve organs from donors and improve functionality, leading to better outcomes for the recipient.[9 10] This hypothesis is supported by a small randomised prospective study in DBD donors conducted in Finland that found patients receiving a heart transplant from donors that had received simvastatin had a striking reduction in markers of early heart injury, an improvement in early cardiac function and a reduction in early rejection rates.[11] The study also found that statins led to a significant reduction in liver injury (transaminase release on day 7) and a non-significant improvement in lung recipients. There was no difference in early or 1-year survival because the study was not powered for these clinical outcomes. Importantly, there were no safety concerns in any organ recipient group.

A further small study has been published from a group in Sicily. Liver donors were randomised to receive the same drug and dose, simvastatin 80 mg. There was a significant improvement in early allograft function and 6-month survival of recipients who received livers from treated donors compared to those who received livers from the control, untreated donors.[12]

Need for a trial

A randomised, controlled trial of simvastatin in addition to standard donor management is needed primarily to determine the effect on patient-centred clinical outcomes in cardiac recipients and to explore secondary outcomes in lung, kidney, liver and pancreas recipients. SIGNET (Statins for Improving orGaN outcomE in Transplantation) is the first national organ donor intervention trial run in the UK.

Delivery of this trial will determine whether giving DBD organ donors a single dose of simvastatin is beneficial for transplant recipients and will contribute towards building the national infrastructure and capacity for interventional research in organ donation and transplantation leading to more high-quality organs available for transplantation.

AIMS AND OBJECTIVES

SIGNET will evaluate whether the treatment of potential organ donors with simvastatin added to protocolised care after diagnosis of death by neurological criteria improves outcomes in patients undergoing transplantation. The specific objectives of this trial are to determine if:

- Simvastatin given to the donor confers an improvement in clinical outcomes in cardiac transplant recipients.
- Simvastatin given to the donor has a beneficial effect on other solid organs, particularly the liver and lung.
- Simvastatin is safe in all organ transplant recipients (heart, kidney, lung, liver, pancreas and isolated pancreatic islets).

TRIAL DESIGN

SIGNET is a multicentre, single-blind prospective, group sequential, randomised controlled trial. We aim to include 474 heart transplant recipients from a total of 2600 recruited donors from intensive care units (ICUs) within NHS Trusts with the highest organ donation potential in England, Scotland, Wales and Northern Ireland. A minimum of 89 NHS trusts are expected to participate. Recruitment commenced in September 2021 and will continue for a minimum of 4 years with a 12-month follow-up period for recipients. Recipient follow-up will only use routinely collected data from the UK Transplant Registry (UKTR). The trial will end 15 months after the final donor has been recruited, to allow for the 12-month UKTR follow-up data to be collected for all recipients. Two interim analyses for harm, benefit or futility are incorporated in the design and sample size calculation. These will be carried out after 50% and 75% of the target number of heart transplants have been followed for 30 days.

METHODS

Eligibility criteria

Potential donors will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria detailed below. There will be no exceptions to eligibility requirements at the time of randomisation.

Inclusion criteria

- A patient within a recruiting ICU.
- Patient diagnosed dead using neurological criteria.
- Consent for organ donation in place, as defined by the Human Tissue Act and accompanying legislation and Codes of Practice.
- Study-specific consent from the donor family.

Exclusion criteria

- Aged <18 years.
- Planned donation after cessation of circulation (DCD).
- Known donor allergic hypersensitivity to simvastatin.

Recruitment and consent

Consent for organ donation, and any research included within the organ donation process, is a specialist area of clinical practice and, therefore, SIGNET has been planned in partnership with NHS Blood and Transplant (NHSBT) to enable trial recruitment to form a part of the usual clinical care of donors and their families. The specialist nurse for organ donation (SNOD) has the required training, skills and knowledge to judge how and when to approach families to consider research within the complex organ donation process and has extensive training in consent to fulfil their duties as outlined in the Human Tissue Act.

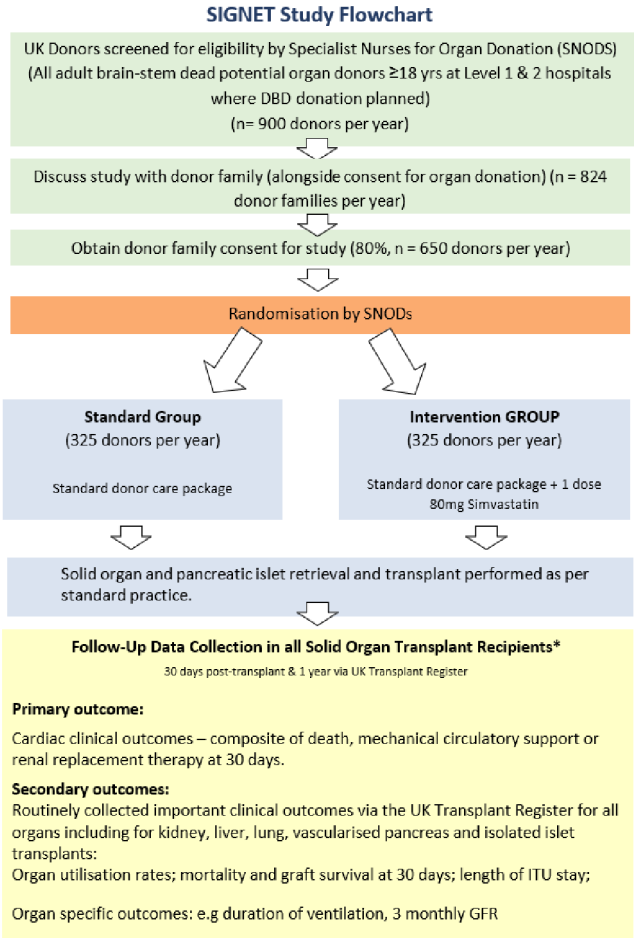

Figure 1 SIGNET study flow chart. SIGNET, Statins for Improving orGaN outcomE in Transplantation; ITU, Intensive Therapy Unit; GFR, Glomerular Filtration Rate.

The SNODs receive training on the SIGNET trial protocol including the key principles of Good Clinical Practice (GCP) and seek specific study consent from donor family members or legal guardians. It is possible that the trial intervention will be more effective the earlier it is given following the diagnosis of death.[13] Considering and prioritising the needs of donor families, ICU staff and the organ donation process, SNODs should seek to reduce the elapsed time between diagnosis of death, approach for organ donation consent, research consent, randomisation and study intervention as much as possible (figure 1). This aligns with NHSBT operational guidance which seeks to minimise the duration of the organ donation process after diagnosis of death.

Consent in the organ donation process is regulated by the Human Tissue Act, and implemented by NHSBT in conjunction with operational practices and the HTA code of practice. There is no mechanism for patients to record their views on research within the Organ Donor Register, and consent is required for research from the next of kin as defined by the HTA code.

The rights of the patient (in the case of SIGNET, the patient's next of kin as defined in the Human Tissue Act)

to refuse to participate in the trial without giving a reason will be respected. Should a participant's next of kin withdraw consent, data obtained up to the point of withdrawal will be kept and included in the analysis.

Potential recipients on the organ transplant waiting list will be provided with a letter and information sheet informing them of the study and how their data will be used. Consent will not be sought from recipients; they will not be known at the time of randomisation and when the organ donors receive the intervention, and we do not anticipate risk to recipients or from the administered intervention remaining active in the recipient.

Randomisation

A centralised web-based randomisation system (Sealed Envelope) will be used and randomise in a 1:1 ratio using permuted blocks of varying, undisclosed size and stratified according to whether the donor was receiving statin therapy at ICU admission.

The ICU and organ donation team caring for donor and family will not be blinded to randomisation. If the patient is randomised to receive 80 mg of simvastatin, the intervention will be prescribed and administered by a member of the ICU team as per local hospital policy. Organ retrieval teams, theatre teams and recipient transplant teams will be blinded. A request to reveal the donor intervention allocation can be made by a potential recipient's treating consultant by direct communication with the central study team or directly with the donor site principal investigator.

Co-enrolment

Formal co-enrolment is not required with other concurrent studies in critical care as they will have met their primary endpoint (death) before recruitment into SIGNET. It is important that SIGNET is not a barrier to other research, therefore, retrieved organs may enter studies or technological service improvement projects prior to transplantation, and the recipients of organs may consent to subsequent studies. While formal co-enrolment of patients is not required in such circumstances, data sharing agreements between such studies will be considered on an individual study basis by the Trial Management Group in order to ensure confounding is recognised, reduced or excluded.

Intervention

The intervention to be studied is a single dose of simvastatin (80 mg) in comparison to standard donor management in accordance with NHSBT protocolised care. The 80 mg simvastatin tablet will be crushed well and mixed with 20 mL sterile water. It will then be administered via nasogastric (NG) tube. An NG tube is part of the current NHSBT Donor Care Bundle which represents standard therapy in the SIGNET study.

Primary outcome measures

The primary outcome measure is a composite outcome of death, cardiac mechanical circulatory support or renal replacement therapy within the first 30 days post heart transplant.

A robust and clinically meaningful composite primary endpoint has been chosen, encapsulating all early adverse outcomes post heart transplant. These endpoints were supported by the study patient and public engagement representatives, both donor families and previous transplant recipients, as important to patients. Mechanical support is required to support life if there is significant cardiac injury. It has a very significant effect on 1-year mortality, so is effectively a surrogate for early death. The need for renal support is linked to less severe early cardiac injury and resulting systemic hypoperfusion. It again is linked to both 1 year and much later mortality.[14]

SECONDARY OUTCOME MEASURES (INCLUDING ORGAN SPECIFIC)

All organs

- Organ utilisation rate—the proportion of organs offered that were transplanted, for each organ separately.
- 30-day, 3-month and 12-month graft survival.
- 30-day, 3-month and 12-month patient survival.
- Length of Intensive Therapy Unit (ITU) and hospital stay, with the exception of kidney recipients as these data are not collected on the UKTR.

Cardiac: secondary outcomes

- Proportion of recipients requiring cardiac mechanical circulatory support up to 30 days.
- Proportion of recipients requiring renal replacement therapy up to 30 days.
- 30-day patient survival.
- 3-month and 12-month number of treated rejection episodes.

Kidney

Primary outcome: 12-month estimated glomerular filtration rate, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Secondary outcomes:

- Proportion of recipients with delayed graft function (need for dialysis in first 7 days).
- 3-month and 12-month number of treated rejection episodes.

Liver

Primary outcome: 3-month graft survival.

Secondary outcomes:

- Number of days ventilated.
- Proportion of recipients with individual postoperative complications—hepatic artery thrombosis, portal vein thrombosis, Inferior vena cava (IVC)/hepatic vein occlusion, haemorrhage requiring reoperation, biliary tract leaks, biliary tract stricture requiring intervention.

- 12-month serum creatinine, bilirubin and alkaline phosphatase.

Lung

Primary outcome: 3-month patient survival.

Secondary outcomes:

- 12-month FEV1 (both absolute and % predicted).

Solitary pancreas and simultaneous pancreas-kidney

Primary outcomes: 3-month pancreas graft survival.

Secondary outcomes:

- Proportion of recipients with initial graft function.
- 3-month and 12-month number of treated rejection episodes.
- Causes of graft loss.
- Proportion of recipients with pancreatitis up to 3 months.

Pancreas islets

Primary outcomes: 3-month meal tolerance test stimulated C-peptide.

SAMPLE SIZE

The primary outcome is a binary composite outcome in heart transplant recipients, as described in the 'Primary outcomes measures' section. UK data from adult DBD heart transplants between April 2016 and March 2019 showed the event rate of this composite outcome was 51.4%. This study is designed to have 90% power to detect a reduction in this composite outcome to 36.0% (a relative risk of 0.7, informed by the Finnish study[11]) using a 5% level of significance and a two-tailed test.

A group sequential design with O'Brien Fleming stopping boundaries has been used to allow the data monitoring committee (DMC) to review the primary outcome for evidence of harm, benefit or futility after 238 and 356 heart transplant recipients have been followed up for 30 days. Allowing for the interim analyses in this way, the required sample size is 474 heart transplants in total. Using data on the proportion of DBD donors who proceed to heart transplant, and a small loss to follow-up rate of 3%, we need to recruit 2600 donors in total.

STATISTICAL CONSIDERATIONS

The primary outcome will be analysed using a mixed logistic regression model, with adjustment for whether the donor was receiving statin therapy at ICU admission and allowing for correlation in recipient outcomes within transplant centres by including a random effect term for transplant centre. The OR, CI and p value for the treatment arm term in this mixed effect model will be the primary analysis.

The three elements of the composite primary outcome will also be assessed as individual secondary outcomes. Other binary outcomes will be analysed using a mixed logistic regression model or competing risks framework as appropriate. Organ utilisation will be analysed for each organ separately using a logistic regression model with adjustment for the use of statin therapy at ICU admission. Three-month and 12-month patient and graft survival will be presented using Kaplan-Meier plots and analysed using Cox proportional hazards regression.

Other outcomes will be presented as mean and SD, or median and IQR as appropriate and analysed using mixed linear regression, Poisson regression, Fine and Gray models or non-parametric methods as appropriate. All organ outcomes will be adjusted for whether the donor was receiving statin therapy at ICU admission and a random effect or frailty term for transplant centre. The kidney transplant outcome analyses will use a cross-classified model to allow for non-nested random effects for transplant centre and donor. Adjustment for other risk factors (published in NHSBT organ-specific reports) will be carefully considered for highly prognostic factors for each organ separately and specified in the statistical analysis plan in advance.

LINKED STUDIES

A separate study will investigate the mechanistic effect of simvastatin on donor immunological profiles using plasma samples from donors in both control and intervention arms of the SIGNET study, which will be collected via an existing national biobank (Quality in Organ Donation).[15] A qualitative study of the donor family and clinical team experience of donor interventional studies is being conducted.

DATA MANAGEMENT

Limited information regarding eligibility, consent, randomisation, treatment and safety in the donor is collected onto paper source data forms by the SNOD and then entered into the study database by the local research teams. The source data form is completed for all donors and the original will be stored at site.

The SIGNET database uses MACRO software provided by Ennov for its database which is Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) part 11 and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) - Guideline for Good Clinical Practice (GCP) compliant. The MACRO database is specifically designed to collect and store clinical trial data and provides the tools to review data and raise queries to site staff to ensure data collection is as accurate as possible before data extraction.

Clinical and safety outcomes in organ recipients from randomised donors will be collected through routinely collected data submitted to the UKTR (figure 2). All UK organ recipients' clinical outcome data are submitted even if patients transition between transplant centres. The registry is held by NHSBT and outcomes are pseudonymised for analysis. This oversight also enables ongoing monitoring of recruitment figures and data quality.

Donor:

Timepoint	Enrolment	Allocation	Post-Allocation			
	T_{-1}	T_0	T_1	T_2	T_3	T_4
ENROLMENT						
Eligibility Screen	X					
Informed Consent	X					
Randomisation/Allocation		X				
INTERVENTIONS						
Simvastatin 80mg in addition to standard donor management protocol		X				
Standard donor management protocol only		X				
ASSESSMENTS						
Donor Demographics	X					
Donor Medical History	X					
Intervention Data		X	X			
Organ Utilisation			X			

T_{-1} – Screening

T_0 - Baseline

T_1 - At organ retrieval / transplantation

T_2 – 30 days following transplant

T_3 –3 months following transplant

$T_4$12 months following transplant

Recipient:

Timepoint	Enrolment	Allocation	Post-Allocation			
	T_{-1}	T_0	T_1	T_2	T_3	T_4
ENROLMENT						
All patients on organ waiting list given recipient information	X					
INTERVENTIONS						
Organ transplant		X				
ASSESSMENTS						
Recipient Clinical Outcome				X	X	X

T_{-1} – Screening

T_0 - Baseline

T_1 - At organ retrieval / transplantation

T_2 – 30 days following transplant

T_3 –3 months following transplant

T_4- 12 months following transplant

Figure 2 Trial assessment schedules.

MONITORING

The DMC comprises three clinical specialists and one statistician all entirely independent of sponsor and study team with no competing interests. The DMC has access to unblinded data if required and meets regularly to provide recommendations to the chair of the Trial Steering Committee (TSC), including early closure of the study should they have concerns. Members of the DMC receive DMC reports ahead of meetings and receive reports in a coded fashion and only unblind themselves if they see a need.

Safety reporting for SIGNET refers only to the donor; all clinical outcomes in recipients are secondary outcomes for the study. Serious adverse events, deemed unexpected and related to research procedures, are entered into the database and reported within 24 hours of the local research team becoming aware of the event. Likewise, any protocol deviations or serious breaches of the protocol or GCP should be raised to the study team within this time frame.

Patient and public involvement and engagement

Patient and public involvement and engagement (PPIE) in the development of SIGNET emphasised the value of reducing early post-transplant morbidity which has fed into the study outcomes. The study has a dedicated PPIE panel and PPIE members who sit on the TSC to oversee the study on an ongoing basis and provide input into donor family and recipient-facing materials and to provide a lay perspective to the management of the trial and its dissemination.

ETHICS AND DISSEMINATION

Ethics

SIGNET received a favourable opinion from the London, Queen Square Research Ethics Committee (Ref: 21/LO/0412). The trial has Health Research Authority approval (IRAS: 288722) to run in the UK and is adopted onto the UKCRN portfolio (CPMS 49404). It should be noted that following discussions with the Medicines and Healthcare products Regulatory Agency, it was agreed that SIGNET was not a Clinical Trial of an Investigational Medicinal Product. This is because although the intervention involves a study medication, it is not a trial of that medication in a research participant, but rather a study of the effect of the addition of that medication to a standard clinical protocol measuring its effects on a specific organ. There is no subsequent medication clinical effect on the recipient, other than the impact on the organ prior to transplant. All the organ outcomes are being measured in the recipient.

Following approval of substantial amendment 1 in January 2023, the current protocol is version 2 (7 December 2022).

We anticipate that results generated from SIGNET will be presented at conferences and published in a high-impact, open-access journal.

Confidentiality

Participants will be identified by an anonymous trial-specific number. The participant's NHSBT donor ID will be collected in a restricted part of the trial database that is only accessible to the independent statistician and will be used for linkage with other donor data and to access transplant recipient follow-up data. Individual participants will not be identified in the resulting publications and presentations from the trial. This trial will comply with the UK Data Protection Act (2018) and the General Data Protection Regulation.

Access to data and dissemination

Custody of the final data set will reside with the chief investigators (CIs) and NHSBT CTU (for audit purposes) and study results embargoed and not disseminated until authorised by the CIs and TSC. Access to the final data set for additional analyses will only be permitted under the agreement of the TSC. Final manuscripts and presentations will be approved by the CIs and TSC prior to publication. Similarly, any subsequent substudy analysis will require authorisation by the CIs and TSC prior to publication. Substudy manuscripts must not be published prior to the publication of the main study.

Findings from the study will be publicly available and disseminated locally and internationally through manuscript publications in peer-reviewed journals and conference presentations at national and international platforms.

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Contributors JD and DH conceived the study and are guarantors for the overall content. PM, AE, HT, DK, JD and DH drafted the manuscript. JD, DH, AE, HT, DK, KK, CJEW, DFM, GAM, NSS, AF, JS, HY, AF, JB, MS, RP, RH and EL contributed to the study design, refinement and implementation of the protocol and approved the manuscript. DH and JD are joint chief investigators.

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Competing interests JAMS has participated in a Scientific Advisory Board for Mogrify CJEW has received honoraria from Organox.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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