SINATRA Study

SkIN hydrAtion evaluation with TeRAhertz scanning

PROTOCOL

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Protocol Amendments

Amendment Number	Protocol Version	Date of Amendment	Date of Approval
0.1	1.1	07.12.2021	16.12.2021
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SA 1	2.0	08.04.2022	19/05/2022

Confidentiality statement

All information contained within this document is regarded as, and must be kept, confidential. No part of this document may be disclosed to any Third Party without the written permission of the Chief Investigator and/or Sponsor.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research, the ICH Good Clinical Practice guidelines and the Sponsor'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 publically 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.

For and on behalf of the Study Sponsor:

Signature: Date:

Name (please print):

Ceri Jones

Position:

Head of R&D

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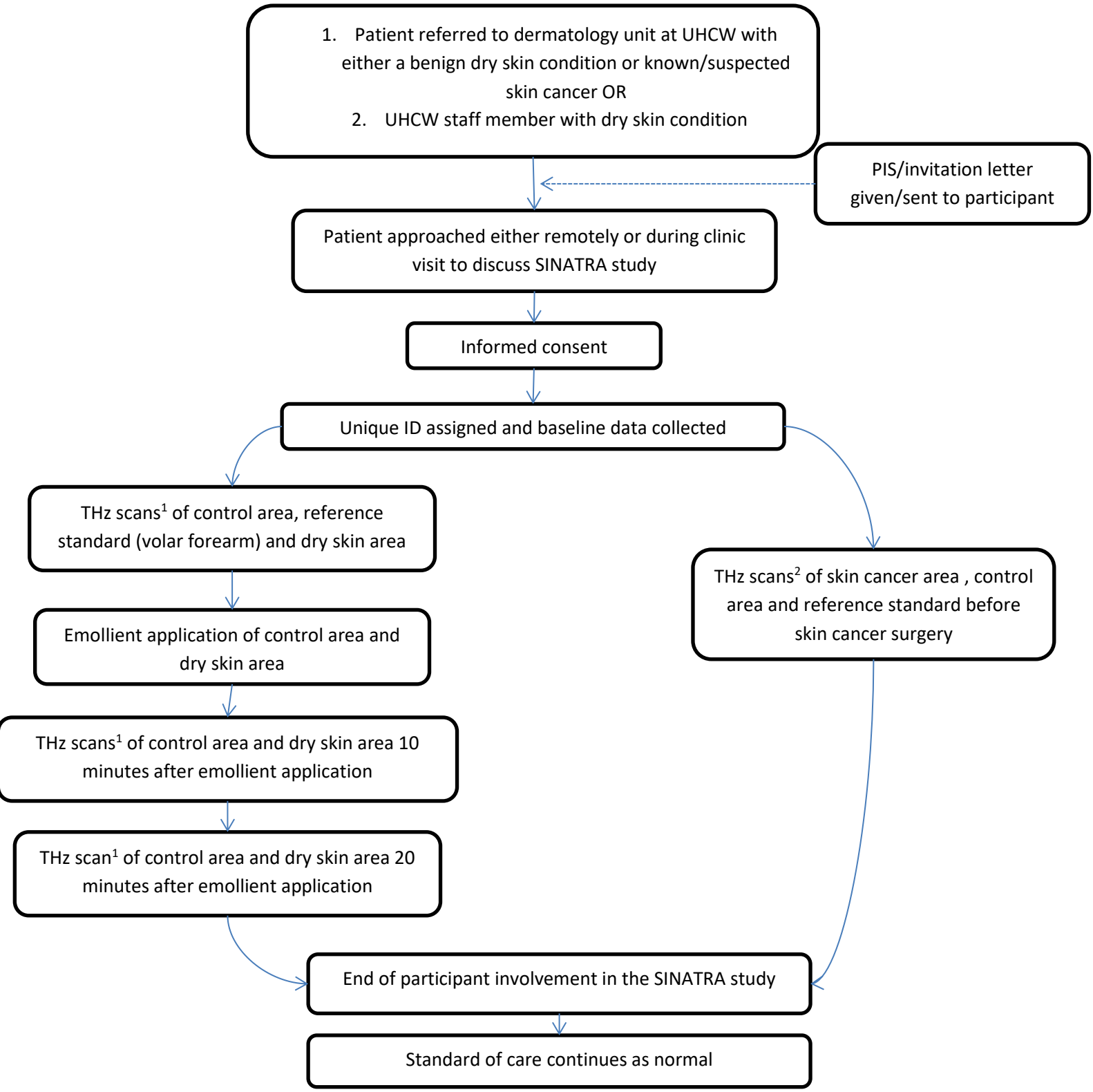
STUDY SUMMARY

Full study title	SkIN hydrAtion evaluation with TeRAhertz scanning
Short study title	SINATRA Study
Study aim	Pilot study to confirm feasibility, test recruitment, trial procedures and refine intervention delivery.
Study design	Single centre, non-randomised, Pilot trial
Study participants	Patients with suspected/confirmed skin cancer and patients with benign dry skin conditions
Study arms	1. Benign dry skin condition group 2. Skin cancer group (either confirmed basal cell carcinoma and/or suspected malignant melanoma)
Sample size	150 (ratio of 2:1 so 100 in the skin cancer group and 50 in the benign dry skin condition group) Within the skin cancer group we will aim for 50 basal cell carcinoma patients and 50 malignant melanoma patients
Planned study period	24 months
Planned recruitment start date	15/03/2022
Planned recruitment end date	15/03/2023
Planned study end date	30/03/2024
Objectives	• To undertake a feasibility study • To assess skin hydration and confirmed/suspected skin cancer water content with terahertz imaging.
Primary Objective	The primary objective will be to explore the feasibility, test recruitment, trial procedures and refine intervention delivery
Secondary Objective	To explore if Terahertz skinometry can quantify skin hydration and will show an increase in skin water content after application of an emollient in dry skin conditions. To explore if Terahertz skinometry can quantify skin hydration and may indicate the presence of residual basal cell carcinoma after primary excision, or the localised inflammation caused by melanoma skin cancer.

Key Words: **SKIN; CANCER; TERAHERTZ; IMAGING; DIAGNOSIS; NOVEL**

Figure 1: Participant Flow Chart



[1]There will typically be 7 quality THz scans in this arm of the study. Areas of interest may be scanned up to a maximum of 3 times at each time point in order to ensure a clear image is received.

[2]There will typically be 3 quality THz scans in this arm of the study. Once identified, each area will be scanned up to a maximum of 3 times to ensure a meaningful datasets acquired. If multiple cancerous areas are identified, the one that gives the clearest image will be chosen. This may involve scanning multiple cancerous areas before a decision is made as to which area is most suitable to pursue.

Table 1: Schedule of Events – Skin Cancer Group

Procedure	Screening	Study visit 1* – before surgery	Surgery	Post-surgery
Eligibility Assessment	X[1]			
Invitation to take part	x			
Informed consent		X		
Baseline data collection		X		
Medical History		X		
Current Medications		X		
THz scan of control area		X		
THz scan of cancer area		X		
THz scan of reference standard (volar forearm)		X		
Skin surgery			X	
Histology results				X
Adverse events		X	X	X

Table 2: Schedule of Events – Benign Dry Skin Condition Group

Procedure	Screening	Visit 1* – before emollient application	Emollient application to dry skin area and control area	Visit 1* – 10 minutes after emollient application	Visit 1* – 20 minutes after emollient application
Eligibility Assessment	X[1]				
Invitation to take part	X				
Informed Consent		X			
Baseline data collection		X			
Medical History		X			
Current Medications		X			
THz scans of		X			

reference standard area (volar forearm)					
THz scans of control area		X		X	X
THz scans of dry skin area		X		X	X
Emollient application of dry skin and control area			X		
Adverse events		X	X	X	X

[1] It will be our endeavour to screen prospective participants before there scheduled visits at the dermatological clinic however, considering this is an observational study prospective participants can be screened/recruited on the day they visit (baseline) the dermatological clinics for their scheduled appointments.

Contents

LIST OF ABBREVIATIONS

2WW	Two-week Wait
BCC	Basal Cell Carcinoma
CCG	Clinical Commissioning Group
CI	Chief Investigator
CRF	Case Report Form
CRRS	Clinical Results Reporting System
CT	Computed Tomography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ID	Identification
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISF	Investigator Site File
NHS	National Health Service
NHS R&D	National Health Service Research & Development
PC	Personal Computer
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
R&D	Research & Development
RCT	Randomized Control Trial
REC	Research Ethics Committee
SC	Stratum corneum
SINATRA	SkIN hydrAtion evaluation with TeRAhertz scanning
SOP	Standard Operating Procedure
THz	Terahertz
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHCW	University Hospitals Coventry and Warwickshire NHS Trust
UoW	University of Warwick

STUDY PROTOCOL

SINATRA Study: **S**k**IN** hydr**A**tion evaluation with **T**e**RA**hertz scanning

1. INTRODUCTION

1.1 Background

Medical imaging commonly involves the use of radiation, such as x-rays, that can give detailed images of internal structures of the body but can carry a small risk of tissue damage due to the radiation involved. As such, the number of x-rays and computed tomography (CT) scans that an individual can have has to be minimised. Methods have recently been developed that make use of electromagnetic radiation for imaging purposes at terahertz (THz) frequencies, the region of the spectrum between millimetre wavelengths and infrared. Terahertz spectroscopic imaging uses low power levels such that adverse effects on tissues are insignificant and is safe for in vivo imaging of humans [1]. The terahertz region is between the radio frequency region and the optical region generally associated with lasers. Both the IEEE RF safety standard and the ANSI Laser safety standard have limits into the terahertz region. The focus of this project is to investigate THz spectroscopic imaging as a new and powerful tool for analysing skin properties, termed “THz skinometry”. The novelty in this project lies in tailoring the instrumentation and algorithms of THz scanning to accurately measure properties of human skin (e.g. hydration levels and skin thickness) in vivo. The customised non-contact and pressure-controlled contact THz probes developed will be able to do spectroscopic measurements of skin in vivo at the molecular level. This will be the first demonstration of in vivo THz imaging of skin globally and will facilitate quantitative characterisation of skin in a way that has hitherto not been possible and could lead to a step change in THz technology usage (similar to that currently used in airport security scanners).

1.2 Proposed study

The SINATRA study is pilot study with a primary aim to explore the feasibility of the trial methodology. In addition, secondary objectives of the study will investigate if THz light is able to detect subtle differences in skin hydration and their clinical relevance. Due to the unprecedented sensitivity of THz light to skin hydration, we will also investigate if different skin types have a preferential uptake of certain emollients. This would include dry skin conditions such as eczema, psoriasis and post-operative scars. This will give us information on how to optimise the types of emollients used in future development of new moisturisers and sunscreens. This is already under investigation in a cohort of volunteers with unaffected skin (unpublished pilot study data, University of Warwick). Additionally, as part of the SINATRA study, we will investigate if THz imaging is able to detect subclinical (invisible) skin cancer (residual basal cell carcinoma (BCC)) and enhance the diagnosis of suspected skin cancer (malignant melanoma) in vivo. Skin cancer is known to produce a localised inflammatory reaction and microscopic swelling and so the changes in skin hydration may be able to be objectively measured by THz skinometry.

Terahertz scanner (Investigational Medical Device) and safety:

Terahertz (10^{12} Hz) pulsed imaging is a new technique with high resolution and has only emerged recently as a potential new clinical tool for medical imaging. It is a safe imaging modality as the light is non-ionising – it has a million times lower energy than an x-ray and thus doesn't have enough energy to cause ionisation. The power levels used in the THz systems in this study are also very low such that there are no lasting effects. In particular, our *in vivo* THz imaging systems have a peak power less than 40mW and average power intensity less than 4 $\mu W/cm^2$. Studies by Hough et al [2] have shown that even using peak power 50,000 times higher and an average intensity 30 times higher does not cause any change in gene expression. Therefore, power levels used in our THz in vivo imaging systems are safe and have no known side effects or risks

1.3 Study population

The SINATRA study will collect preliminary pilot data from participants in a two-arm feasibility observational study.

1. One arm will consist of 100 patients with known or suspected skin cancer (skin cancer defined as: incompletely excised BCC with histologically proven radial margin involvement; biopsy proven BCC, or pigmented lesions suspicious of malignant melanoma). Images will be taken in the clinic prior to planned skin surgery and later compared to the formal histology results after the primary (melanoma) or residual (BCC) tumour has been removed.
2. The second arm will consist of 50 patients with benign dry skin conditions (eczema, psoriasis, skin grafts, scars etc.) and will compare the water content of their skin before and after application of a propriety emollients in common usage (e.g. E45®, Aveeno®, Doublebase®). This will add to the existing dataset that has been recorded from healthy non-patient volunteers (unpublished data, University of Warwick). This may help to guide patient-specific emollient selection in the future.

This will add to the knowledge base to define the appearance of skin cancers under THz skinometry. The spectroscopic findings will not influence the established management that will have been planned in conjunction with a Consultant Dermatologist or Plastic Surgeon and the patient.

1.4 Treatment / Intervention

Study arm 1: The study arm of 50 patients with benign dry skin conditions will undergo scans with the THz skinometer and will compare the water content of skin before and after application of propriety emollients in common usage (e.g. E45®, Aveeno®, Doublebase®). Participants will have a THz scan of the dry skin area, a control area if possible (similar site but without the skin condition) and a standard reference area (volar forearm with no skin condition present if possible). Then they will apply their emollient and wait 10 minutes to have another scan of the control area and dry skin area. Finally there will be another 10 minute wait before having the final scans of the control area and dry skin area. There will be a minimum of 6 quality scans in total for this group (if the volar forearm is used as the

control area as well as the reference standard). Most likely there will be 7 scans in total (as the reference standard only needs to be measured once)However more scans may be required in order to identify the most suitable area to scan. E.g. if a patient has multiple spots of dry skin on their body, the team may attempt to scan one area but find it is difficult to access and that it does not produce a clear image. In this instance the team would select another dry skin area which is easier to position onto the THz Skinometer. At each time point (pre-emollient and 10 & 20 minutes post emollient) there will be a maximum of 3 scans performed on the dry skin and control area. This is to ensure a meaningful dataset is obtained at each time point.

Study arm 2: The arm with 100 patients with known or suspected skin cancer will have a scan with the THz skinometer in the clinic prior to their planned skin surgery. They will be scanned on the cancerous area, a control area and a reference standard area (the volar forearm) for a minimum of 3 quality scans. In the event that the reference standard and control area are the same, then the participant will only have a minimum of2 quality scans. The purpose of the reference standard area scan is to act as a calibration point and so we can compare a between subject variable as well as the within subject variable from the cancer/control area. If a participant has multiple potentially cancerous areas on their body, the team will decide which of these areas to scan for the study. If it occurs that the chosen area is too difficult to scan/doesn't produce a clear enough image then a different cancerous area will be selected. There will be a maximum of 3 scans conducted at each of the cancerous area, control area and reference standard area in order to obtain a meaningful dataset. Later the results of the THz scan will be compared to the formal histology results after the primary (melanoma) or residual (BCC) tumour has been removed.

For patients with multiple skin conditions (i.e. multiple dry skin or cancerous locations on the body), we will select the area that is most practical to scan and can make good contact with the scanner.

1.5 Pre-clinical data

In vivo THz images from a case study of patients with BCC in 2004 [1] suggested that it should be possible to detect skin cancer hidden beneath the skin using THz imaging. Spectroscopic studies by Emma MacPherson (EM; Co-investigator) and her colleagues in Cambridge in 2006 showed that the fundamental THz properties of freshly removed (excised) skin cancer tumours are statistically significantly different from healthy tissue [2] and it is thought that the differences are primarily due to changes in water content of the tissue. The high sensitivity of THz light to water also means that the THz signal is strongly attenuated and has a very limited penetration depth in tissue [3] – thus THz scanning would experience great difficulty in detecting deep tumours. The penetration depth depends on the signal-to-noise ratio of the THz imaging system, therefore efforts to improve the signal processing and/or the THz instrumentation have been made. Since then, EM has been investigating the underlying THz image contrast mechanisms [4,5] as well as developing new algorithms and approaches to improve the accuracy of sample characterisation [6,7] as well as accelerating THz image data acquisition. This more recent work is pushing the state-of-the-art in THz in vivo imaging, both in accuracy and speed. This, crucially, means we are now

better equipped to do THz imaging in vivo studies and we have even been able to account for the pores of skin being blocked (occluded) by the imaging window for the duration of the THz measurement. This 'occlusion' process means the skin cannot breathe normally and water accumulates in the outer most layer of skin, the stratum corneum (SC) [8]. EM has exploited this phenomenon to pioneer the use of THz imaging to determine rate of water diffusion within the SC during occlusion. EM has also been developing in vivo imaging instrumentation techniques and identifying the key variables and parameters such as contact pressure and occlusion duration [9]. EM's latest results show that the refractive index of the skin increases both with increasing pressure and increasing occlusion time. These results will be used to develop the THz skinometer and accompanying characterization algorithms, within this study. EM's findings show how THz imaging can be used to measure the hydration profile and water diffusivity of skin and this is the basis of the theory that will be further developed in the SINATRA study to evaluate the penetration and durability of emollients and sunscreens in different skin types. The pilot data collected in the SINATRA trial will be valuable in developing a larger trial leading to a transformative improvement in prevention and treatment of skin cancer and better moisturisation strategies for other skin conditions.

1.6 Clinical data

There is limited clinical data available due to the novelty of this imaging modality. This data includes a single case study report investigating scarred tissue [5] and a study of five *in vivo* basal cell carcinoma (BCC) skin cancers [1]. Good contrast was seen between normal tissue and regions of tumor in terahertz pulsed imaging of BCC. These changes are consistent with higher water content. These results account for the contrast seen in terahertz images of BCC and explain why parameters relating to the reflected terahertz pulse provide information about the lateral spread of the tumor. No adverse effects were recorded.

2. RATIONALE

2.1 Aims and hypothesis

The primary aim of SINATRA study is to explore the feasibility of trial methodology

Justification:

The SINATRA trial is an observational study utilising a novel technology thus it is prudent that we collect feasibility data which can inform the development of a definitive trial. We hope that this novel technology, if proven effective, may allow the assessment of emollients and may lead to personalised medicine for the treatment of dry skin conditions. There is also no objective and accepted way to diagnose skin cancer *in vivo* (without biopsy). Current methods are subjective and require training and experience to improve accuracy (clinical examination and dermoscopy). This can result in unnecessary biopsy of benign lesions increasing the risk of patient harm and healthcare costs.

The risk to the patient who is having the scan with the Terahertz (THz) skinometer is negligible. It uses non-ionising radiation, at lower energy that visible light. There is a risk of skin reaction when an emollient is applied. To mitigate this risk, participants will be requested to use emollients they have used previously and they will be requested to bring their own moisturising cream. The scan time is short and painless. The skin area of interest will be placed on the scanner at low pressure. The scanner will be cleaned with standardised clinical cleaning agents between patients. There will be no additional risk compared to standard practice. Patients will be treated in accordance with institutional coronavirus (COVID-19) clinical risk assessments and practice.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

The primary objective will be to explore the feasibility, test recruitment, trial procedures and refine intervention delivery.

3.2 1. Secondary objectives

- To explore if Terahertz skinometry can quantify skin hydration and will show an increase in skin water content after application of an emollient in dry skin conditions.
- To explore if Terahertz skinometry can quantify skin hydration and may indicate the presence of residual basal cell carcinoma after primary excision, or the localised inflammation caused by melanoma skin cancer.

3.3 Primary endpoint/outcome

Feasibility outcomes measures:

- Number of patients screened, eligible, recruited, withdrawn and retained
- Willingness of participants to participate in the trial

3.4 Secondary endpoints/outcomes

Physiological and clinical outcomes: The secondary outcome is an objective difference in skin hydration between normal skin, benign skin conditions, skin containing residual basal cell carcinoma and skin containing malignant melanoma. The secondary research end point will be after the comparison of scan data with formal reported histological analysis as part of the standard skin cancer management pathway.

4. STUDY DESIGN

A pragmatic, non-randomised, single-centre, feasibility study

5. STUDY SETTING

The SINATRA study will be run within the Department of Dermatology, University Hospitals Coventry and Warwickshire NHS Trust.

Prospective participants will include UHCW staff members and patients suffering from dry skin conditions and known and suspected skin cancer. The patients will be recruited from scheduled Dermatology out-patient clinics including routine general Dermatology clinics (study arm 1: dry skin conditions), two week wait (2WW) urgent Dermatology clinics for suspected skin cancer, and joint clinics run between Dermatology and Plastic Surgery (study arm 2: known or suspected skin cancer). UHCW staff members will be recruited via posters which will be displayed within UHCW and circulated to all staff in internal news bulletins.

The patients will be identified screened and recruited by delegated research team member (Dermatologists, Plastic surgeons, Research Nurse), and scanned with the THz skinometer by non-clinical scientists (Physicists), within a designated clinical area. All non-clinical scientists will have honorary contracts at UHCW, be on the delegation log and have up to date GCP training.

6. ELIGIBILITY CRITERIA

Prospective participants are eligible to participate in the trial if they meet the following criteria

6.1 Inclusion criteria

Study arm 1 (benign dry skin condition) – patients or NHS staff:

- Aged 18 years and over
- Diagnosed with dry skin conditions (e.g. eczema, psoriasis, scars etc.)
- Capacity to give informed consent

Study arm 2 - patients only:

- Aged 18 years and over
- Confirmed or suspected skin cancer (incompletely excised BCC with histologically proven radial margin involvement, biopsy proven BCC or pigmented lesions suspicious of malignant melanoma) .
- Diagnosed with an incompletely excised basal cell carcinoma skin cancer (either radial margin involvement on primary excision or following diagnostic punch biopsy).

- Clinically suspicious pigmented skin lesion (suspected melanoma) with a plan for surgical biopsy
- Capacity to give informed consent

6.2 Exclusion criteria

Study Arm 1 (benign dry skin condition)

- Previous allergy or sensitivity to propriety emollients in common usage (e.g. E45®, Aveeno®, Doublebase®etc.).

7. TRIAL PROCEDURES

7.1 Recruitment

Prospective participants will be recruited from scheduled Dermatology out-patient clinics including routine general Dermatology clinics (dry skin conditions), two-week wait (2WW) urgent Dermatology clinics for suspected skin cancer, and joint clinics run between Dermatology and Plastic Surgery. Eligible UHCW NHS Trust employees will also be able to participate in the trial in arm 1 only.

Prospective participants who fulfil the inclusion criteria will be invited to participate in the SINATRA study following their consultation, either by a member of the clinical team or the clinical research team. Initial approach and consultation can happen either before a patients clinic visit or on the day of their visit if contact cannot be made beforehand. Patients will not be randomised as part of this pilot feasibility study.

7.1.1 Patient identification and Screening

Prospective participants will be identified and screened by a member of their direct healthcare team at the time of clinical review or prior to clinical review from referral letters or photographs. As part of screening following data will be collected for all patients who are invited to be part of the study, including those who decline entry to the study:

- patient hospital ID number
- Basic demographical data

Considering the efforts in the Trust to reduce the number of non-urgent patient visits due to the ongoing pandemic. We will endeavor to contact prospective participants either by telephone or email before their scheduled visit to the dermatology clinic to introduce them to the trial. If they are interested in finding out more they will be referred to a member of the study team, who will explain the study and provide the patient with the PIS and invitation letter following which a delegated member of the research team will confirm their eligibility. If the research team cannot contact the patient before their clinic visit, then a delegated member of the research team can approach them on the day of their visit to first introduce them to the study and offer them an invitation letter and PIS. Following this consultation and after the patient has had a suitable amount of time to consider the trial, they can be invited to enter the study and consent can be taken. In addition study posters

placed around UHCW will inform prospective participants (patients & staff members) about the ongoing trial.

7.1 Consent

Prospective participants will be asked to confirm whether they have read and understood the PIS and will be encouraged to ask questions and be provided enough opportunities to discuss before deciding to take part in the study. Patients will be free to discuss the study with friends and family before reaching their decision.

After confirming the patient's eligibility to take part, a qualified member of the research team, who has received training in obtaining informed consent, will obtain consent. Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of SINATRA study and out-with standard routine care at the participating site. The participant will be able to refuse to participate in the study without giving any reasons and this will not affect their standard treatment in any way.

If verbal translation is needed, this will be provided via a hospital interpreter or an independent interpreter or telephone translation services that are used within the University Hospitals of Coventry and Warwickshire NHS Trust.

The consent procedure will be undertaken by a delegated member of the research team and will involve:

- Discussion between the potential participant and an authorised individual who is knowledgeable about the research and about the nature and objectives of the trial and possible risks associated with their participation.
- Presentation of written material (e.g., information leaflet and consent document which must be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements)
- Opportunity for potential participants to ask questions.
- Assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
    - understand the purpose and nature of the research
    - understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - understand the alternatives to taking part
    - be able to retain the information long enough to make an effective decision
    - be able to make a free choice
    - be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
    - where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

Patients who are determined to lack capacity will be excluded from recruitment to the SINATRA study.

Consent will be taken prior to the THz scan. Patients who are identified by the research team may be contacted prior to their scheduled appointment at the clinic to introduce them to the trial. Patients identified on the day of first review will be given appropriate time to decide whether to participate in the SINATRA study.

7.1.2 Payment

Patients who are recruited will be offered £10 travel and parking expenses to compensate for any extra time incurred for involvement in the trial.

7.2 Baseline data

The following information will be collected as part of baseline data:

- Patient hospital ID number
- Unique study ID assigned to participant
- Demographics including : age, sex, ethnicity, height, weight, BMI
- Provisional clinical diagnosis
- Location of area to be scanned

7.3 Trial assessments

After patient recruitment, individuals will have a photo taken of the area of skin to be scanned before being scanned with the THz skinometer. A non-toxic Easi-Mark Surgical Skin Marker will be used to draw around the area to be scanned for image registration (both study arms) and to control the amount of skin product applied in the fixed area (study arm 1 only). This will be performed by a delegated research team member in an appropriate environment as per standard trust policy.

A. **Study arm 1**: A minimum of 6 (most likely 7) readings of the THz skinometer ("scan") will be conducted after measuring the area of interest (AOI) and area of unaffected skin (control area measurement), at the following time points:

   1. Pre-application THz skinometer ("scans") of the AOI and area of unaffected skin, and the reference standard (volar forearm)

2. Post-application scan-I: participant will then be requested to apply emollient used regularly by them to the dry skin and control area, following which after 10 minutes another THz skinometer ("scans") will be conducted of the AOI and control area

3: Post-application scan-II: Repeat scans of AOI and control area will be conducted 10 minutes following the post-application scan-I

Further scans may be required if a clear image is not received upon the first attempt. At each time point each area will be scanned a maximum of 3 times to ensure a clear image is received.
Following the completion of the scans this will be the end of participation in the trial and the patient will continue the standard treatment pathway.

Study arm 2: A minimum of 2 (most likely 3) readings of the THz skinometer ("scan") will be conducted after measuring the AOI, area of unaffected skin (control area measurement) and the reference standard (volar forearm).
As with study arm 1; each area can be scanned up to 3 times to ensure a clear image is received. If a participant has multiple cancerous areas on their body the team will select the area most appropriate/feasible to scan. If they are unable to receive a good image, they will select another area instead.

This will be the end of participation in the trial and the patient will continue the standard treatment pathway. Histological diagnosis will be collected remotely using patient notes/medical records at a later date (typically 2-4 weeks after biopsy) by a delegated research team member.

7.4 End of study definition

The study will close after the final scan on the final participant.

8. STATISTICS AND DATA ANALYSIS

The summary of the study process from approaching a patient about the study to collecting their data at the study visit consists of the following steps

1. Step 1: During a clinic visit, a patient will be approached to check whether they are willing to be screened and enrol in the study. We will record the number of patients that are approached and how many are willing to enrol in the study.
2. Step 2: For each patient willing to enrol, a study visit will be scheduled. A record of whether a patient comes for a scheduled study visit will be kept.
3. Step 3: Eligibility will be assessed during the study visit.
4. Step 4: If a patient is eligible, they will be asked whether they are still willing to be part of the study, that is, whether they consent to be enrolled/recruited in the study.

The process will continue until at least 150 patients are recruited in the study; 50 for benign dry skin conditions group and 100 in the skin cancer group (we will aim for 50 basal cell carcinoma patients and 50 malignant melanoma patients).

Data collected in step 1 will be used to estimate the rate of willingness to enrol in the study. It will be computed as the proportion of approached patients who indicate they are willing to enrol in the study. A conservative estimate for the rate of willingness will combine information in steps 1 and 2, where patients who do not come for the study visit are considered not willing to enrol in the study. Eligibility rate, computed using data in step 3, will be proportion of eligible patients among those assessed for eligibility. Proportion of eligible patients that are recruited will give the recruitment rate. These rates will be computed for the three study groups (benign dry skin conditions, basal cell carcinoma and malignant melanoma) separately.

For all consenting eligible patients, during the study visit, outcomes will be taken for the affected (area of interest) and unaffected (control) parts of the skin. For each group, a paired t-test will be used to compare the means of outcomes (e.g. skin hydration) for affected and unaffected parts. The corresponding mean difference between affected and unaffected parts and 95% confidence interval (CI) will also be reported. For affected parts, using one way analysis of variance (ANOVA), we will test whether the means for the three groups are equal. Pairwise comparisons using independent t-tests will also be performed, with mean difference and 95% CI reported. We will also compare unaffected parts means for the three groups similarly.

Since this is a feasibility study, we will test all hypotheses at 10% significance level. Also, we will not adjust for multiplicity associated with testing multiple hypotheses. However, for it to be worthwhile conducting a future large study to test utility of THz, clear signals (large differences), estimated using mean differences and 95% CIs, will need to be observed in this feasibility study.

8.1 Sample size consideration

The target is to recruit at least 50 patients for each of basal cell carcinoma group, malignant melanoma group and benign dry skin conditions group. We anticipate at least 80% of patients who meet eligibility criteria to accept to enrol, that is, recruitment rate is at least 80%. For eligibility rate, we consider the worst case scenario (50% eligibility rate) and low eligibility rate of 20%. We consider three cases of willingness rates (20%, 50% and 80%). Table 1 shows the sample sizes and margins of error (ME), where ME = $1.96 \times \sqrt{\frac{rate \times (1-rate)}{sample\ size}}$. The largest number needed to be approached is 1575 patients for each group. As highlighted in the table, we expect a scenario requiring to approach 630 to be closer to the reality. The largest margin of error corresponds to the recruitment rate at 9.9% so that the 95% CI is 70%-90%. We consider this to precise enough for recruitment rate.

For comparing means, power is lowest for independent t-tests. With 50 patients in each group, assuming a moderate effect size (standardised difference of 0.5), the power is 80% at 10% significance level.

Table 1: Sample sizes and margins of errors

Willingness rate	**20%**	**20%**	**50%***	**50%**	**80%**	**80%**
Eligibility rate	**20%**	**50%**	**20%***	**50%**	**20%**	**50%**
Recruitment rate	**80%**	**80%**	**80%***	**80%**	**80%**	**80%**
Willingness: n†	1575	630	630	252	394	158
ME	2.0%	3.1%	3.9%	6.2%	3.9%	6.2%
Eligibility: n‡	315	126	315	126	315	126
ME	4.4%	8.7%	4.4%	8.7%	4.4%	8.7%
Recruitment: n§	63	63	63	63	63	63
ME	9.9%	9.9%	9.9%	9.9%	9.9%	9.9%

*†Corresponds to number approached to be screened; ‡Corresponds to number screened for eligibility; §Corresponds to number eligible; *Expect reality closer to this scenario.*

8.2 Planned recruitment rate

Approximately 6000 new 2WW referrals for suspected skin cancer are reviewed within the Department of Dermatology at UHCW per year. With over 100 new referrals per week, and a known conversion rate of 2-3% for biopsy proven melanoma, around 2 to 3 new cases of melanoma will be diagnosed per week. Within the study recruitment period, the planned number of patients recruited to both study arms should be achieved. Although a temporary reduction was noted in the referral patterns at the onset of COVID-19, these numbers returned to pre-COVID-19 levels within a matter of months. If a "second wave" or further incidence of COVID-19 causes similar disruption, then possible delays in recruitment may be incurred.

8.2.1 Summary of baseline data and flow of patients

Patient age, sex, location of anatomical area of interest to be scanned and provisional clinical diagnosis will be collected as baseline data. This will be analysed to investigate the recruitment process to improve recruitment during the SINATRA study period and in future similar studies.

8.3 Participant population

The patients will be recruited from scheduled Dermatology out-patient clinics including routine general Dermatology clinics and staff members working at UHCW NHS Trust (study arm 1: dry skin conditions) OR two week wait (2WW) urgent Dermatology clinics for suspected skin cancer, and joint clinics run between Dermatology and Plastic Surgery (study arm 2: known or suspected skin cancer). Patients will be selected based on clinical diagnosis. Patients will not be randomised.

8.4 Procedure(s) to account for missing or spurious data

Data will be collected on the day of recruitment and no further patient data will be collected after this, with the exception of histological results (study arm 2). Histological results are securely stored on the University Hospitals of Coventry and Warwickshire Clinical Results Reporting System (CRRS). As part of a cancer care pathway, these patients are tracked by the Cancer Support Team and Cancer MDT Facilitator to ensure data is not lost.

In the rare event that THz skinometer scan data is lost (e.g. not recorded, deleted in error) then the accompanying patient information will be removed from the SINATRA study.

As part of this feasibility study, a wide range of data is expected, and so spurious data will be included into the study analysis.

9 DATA MANAGEMENT

9.1 Data collection tools and source document identification

Digital scan data will be collected and stored on a dedicated password protected PC or hard drive. Each data set will be assigned a unique Identification Code. Patient identifiable data will be stored in the Study Site File (Patient Hospital Number) on a participant identification log.

Subsequent biopsy results (study arm 2) that will be collected as part of the routine NHS care pathway will be identified from the University Hospitals of Coventry and Warwickshire Clinical Results Reporting System (CRRS) by the Principle Investigator who is a clinical member of NHS staff. The result will be anonymised and linked to the unique patient ID to then be linked to the THZ skinometer data.

9.2 Access to Data

The SINATRA Study data sharing plan is outlined below:

1) Patient recruitment and progress will be updated continuously throughout the timeline of the project via an Institutional website (University Hospitals Coventry and Warwickshire NHS Trust) led by the UHCW Research and Development department and the UHCW Innovation Hub, of which the lead applicant is Clinical Innovation Lead.

2) The Patient and Public Involvement (PPI) group will be updated on patient recruitment in addition to institutional websites, via the Clinical Research Nursing team.

3) Pseudonymised patient data will not be shared outside of the primary study group. This will be used to link the skinometer measurements with clinical histopathological results within the remit of the SINATRA study.

4) Anonymised patient data (e.g. number of patients, age range, sex) will be shared during the final data analysis within the timeline of the project and subsequent public release of data. Anonymised patient data may be shared with future researchers (academic or commercial) at the discretion of the chief investigator if the participant has consented to this.

5) A data-sharing agreement will be used to impose appropriate limitations on the secondary use of the data.

6) The UHCW R&D team, UHCW Innovation team and the University of Warwick (Warwick Ventures) will be informed of all developments where there might be a potential for commercial interest, and in particular prior to any data sharing. It may be necessary to delay data sharing and modify any data sharing plan to ensure that patient benefit can be maximised.

7) The final dataset will consist of anonymised patient metadata (e.g. number of patients, age range, sex) and skinometry measurements.

9.3 Archiving

Following the resolution of queries and confirmation of study close-out by the Chief Investigator, all essential documentation will be transferred to a third-party archiving service, which provides suitable fire and water-resistant facilities. Study files will be archived for a period of 25 years. Access to the study documentation will be restricted to named individuals within the study team with express permission from the Chief Investigator.

10. Safety Monitoring

The THZ scanner is a non-invasive diagnostic tool which emits million times lower energy than an x-ray and thus doesn't have enough energy to cause ionisation. The power levels used in the THz systems in this study are also very low such that there are no lasting effects. In particular, our *in vivo* THz imaging systems have a peak power less than 40mW and average power intensity less than 4 $\mu W/cm^2$. Studies by Hough et al [2] have shown that even using peak power 50,000 times higher and an average intensity 30 times higher does not cause any change in gene expression. Therefore, power levels used in our THz in vivo imaging systems are safe and have no known side effects or risks

Considering, participants will only vary from their usual care at the point of baseline data acquisition. The trial team will therefore not report any of the following events happening 30 minutes after the final THz scan.

10.1 Definitions (from ISO/FDIS 14155)

10.1.1 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional misuse.

10.1.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational device

NOTE 2: This includes events related to the procedures involved (any procedure in the protocol).

NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

10.1.3 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

10.1.4 Investigational medical device

Medical device being assessed for safety or performance in a clinical investigation.

10.1.5 Serious Adverse Device Effect (SADE)

Adverse Device Effect that has resulted in any of the consequences characteristic of a serious adverse event.

10.1.6 Serious Adverse Event (SAE)

Adverse event that:

a) led to a death,

b) led to a serious deterioration in health that either:

1) resulted in a life-threatening illness or injury, or

2) resulted in a permanent impairment of a body structure or a body function, or

3) required in-patient hospitalisation or prolongation of existing hospitalisation, or

4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if: a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalisation for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

10.1.7 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

10.2 Reporting procedures

Participants will have the opportunity to report any events during the baseline data acquisition, but will also direct contact with the trial team by telephone and email to report any events at a later stage.

10.2.1 Reporting of ADEs and AEs

AEs and ADEs could be observed directly when patients undertake baseline measurements. Unscheduled clinic visits will be arranged if further clinical care is required following an AE. All non-serious AEs/ADEs should be reported or documented as soon as possible but no

later than a month on the AE form and then recorded onto the trial database. If the outcome to the AE is serious then an SAE form should be completed. AEs and ADEs reporting will be conducted as per sponsors SOP which comply with the EC Medical Devices Directive (93/42/EEC) and MEDDEV 2.7/3.

10.2.2 Reporting of SAEs/SADEs and USADEs

The EC Medical Devices Directive (93/42/EEC) requires a manufacturer to fully record all adverse incidents that occur during a clinical investigation and include them in the annual reports to the main REC (and MHRA if appropriate). The legal responsibility for reporting SAEs/SADEs lies with the manufacturer or their authorised representative. However, the MHRA also has a voluntary reporting requirement for 'users' of devices i.e. where a device is being used in a trial in which the manufacturer has no involvement, and in this case, the coordinating centre would submit the appropriate reports and also inform the manufacturer of the event.

All SAEs/SADEs and USADEs occurring at the time of baseline data acquisition must be recorded on the SAE form and reported to the Sponsor within 24 hours of the research staff becoming aware of the event. An initial report may be made orally but must be followed up promptly by a detailed written report. SAE form will be completed together with relevant supporting documents, including an assessment of severity, causality and expectedness, as reviewed by the chief investigator or other medical professional. SAE form should be submitted to the sponsor's office at r&dsponsorship@uhcw.nhs.uk.

For each SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial device / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

The seriousness, causality & expectedness of an SAE will be reviewed by the CI for reporting purposes

Relationship to trial procedure	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

11 TRIAL OVERSIGHT

11.1 Role and responsibilities of the Sponsor

UHCW has agreed to act as sponsor for this trial and will undertake the responsibilities of sponsor as defined by the UK Policy Framework for Health and Social Care Research and ICH Good Clinical Practice (GCP). An authorised representative of the Sponsor has approved the final version of this protocol with respect to the trial design, conduct, data analysis and interpretation and plans for publication and dissemination of results. As sponsor, UHCW provides indemnity for this trial and, as such, will be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this trial. The indemnity is renewed on an annual basis and will continue for the duration of this trial.

11.2 Role and responsibilities of the Funder

Funding for this trial is provided by the Cancer Research United Kingdom (CRUK) and the EPSRC. The design and management of this trial are entirely independent of the funder.

11.3 Trial Management Arrangements

This will be a single centre study. The Site Chief / Principal Investigator responsibilities include, but are not limited to:

- Ensuring that the trial is conducted as set out in the protocol and supporting documents
- Delegating trial related responsibilities only to suitably trained and qualified personnel and ensuring that those with delegated responsibilities fully understand and agree to the duties being delegated to them;
- Ensuring that CVs and evidence of appropriate training for all Site staff are available in the Trial Site File;
- Ensuring that all delegated duties are captured in the study Delegation Log;

- Ensuring all Adverse Events are documented and reported promptly to the Trial Manager;
- Accountability for trial treatments at their site;
- Ensuring the trial is conducted in accordance with ICH GCP principles;
- Allowing access to source data for monitoring, audit and inspection;

11.3.1 Trial Steering Committee

Name	Affiliation	Expertise
Chair (TBC)		
Joseph Hardwicke*	**UHCW**	**Clinical**
Emma MacPherson*	**University of Warwick**	**THz Skinometry**

***non-voting member**

The role of the Trial Steering Committee (TSC) will be to provide overall supervision of the trial, in particular with respect to the progress of the trial, adherence to the protocol, patient safety and the review of new information. The TSC has reviewed and agreed the final version of the Protocol. Face to face meetings will be held at regular intervals determined by need, but no less than quarterly. A TSC Charter will be agreed at the first meeting which will detail how it will conduct its business.

11.3.2 Trial Co-ordinator / Manager

The Trial Co-ordinator / Manager will have responsibility for overseeing day to day coordination of the trial and reporting regularly to the TSC. The Trial Manager's responsibilities include, but are not limited to:

- Coordinating protocol development, patient and trial management documents
- Correspondence with study funder and tracking of progress against agreed milestones
- Setting up and maintaining the Trial Master File;
- Ensuring necessary approvals are in place before the start of the trial at each site;
- Providing training to trial personnel;
- Providing data management support; including data input, maintenance of the trial database and raising of queries
- Producing trial progress reports and coordinating TSC meetings and minutes;
- Ensuring data security and quality and ensuring data protection laws are adhered to;
- Ensuring complete records are in place for audit and monitoring purposes;
- Ensuring the trial is conducted in accordance with the ICH GCP;
- Archiving all original trial documents including the data forms in line with UHCW NHS Trust policy

12 MONITORING, AUDIT & INSPECTION

The study will be monitored by the Research & Development Department at UHCW as representatives of the Sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Ethical approval and research governance

The study will be conducted in compliance the principles of the ICH GCP guidelines and in accordance with all applicable regulatory guidance, including, but not limited to, the UK policy framework for health and social care research. Ethical approval for this study will be sought from the Research Ethics Committee combined with Health Research Authority (HRA) approval. No study activities will commence until favourable ethical opinion and HRA approval has been obtained. Progress reports and a final report at the conclusion of the trial will be submitted to the approving REC within the timelines defined by the committee. Confirmation of capacity and capability will be obtained from the R&D department prior to commencement of the study at all participating sites.

13.2 Peer review

This study has been reviewed by the Engineering and Physical Sciences Research Council (EP/S021442/1).

13.3 Public and Patient Involvement

The UHCW R&D Patient and Public Involvement (PPI) Group have reviewed a research abstract for this study and feedback received and used to design the research protocol.

13.4 Data protection and patient confidentiality

The study will comply with the current Data Protection regulations and DPA 2018 and regular checks and monitoring will be undertaken by the Chief Investigator to ensure compliance. Participants will be assigned a unique identifier upon enrolment into the study to allow link-anonymisation of patient-identifiable data. Access to patient identifiable data will be restricted to members of the study co-ordination team who require it for the performance of their role. Electronic data will be stored on password protected encrypted drives and hard copies of study documents will be stored in locked filing cabinets in secure entry-card protected sites.

14 DISSEMINATION POLICY

All data arising from the conduct of this study will remain the property of University Hospitals Coventry and Warwickshire NHS Trust. All efforts will be made to ensure that the

results arising from the study are published in a timely fashion, in established peer-reviewed journals. Results will be disseminated to collaborators, colleagues, health professionals and participants via internal and external conferences and seminars, newsletters, and via interested groups, including local healthcare commissioning groups.

15. INTELLECTUAL PROPERTY

If any IP sensitive findings are uncovered, the Research Team will liaise directly with the Sponsor's IP adviser and an exploitation plan will be developed between the sponsor, funder and manufacturer. This will happen before any sensitive information is released in to the public domain.

16 REFERENCES

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