Monitoring wound status using multi-parameter optical fibre sensors

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SYNOPSIS

Title	Monitoring wound status using multi-parameter optical fibre sensors
Acronym	OFSSWM
Short title	Monitoring wound status using multi-parameter optical fibre sensors
Chief Investigator	Professor Frances Game
Objectives	**Primary:** • To explore the feasibility of using Optical Fibre Sensing System for Wound Monitoring (OFSSWM) in a clinical environment. **Secondary:** • To compare the optical probe from the OFSSWM to conventional measurement devices. The parameters to be assessed are: humidity, ammonia (NH_3), Carbon Dioxide (CO_2), and temperature. • To provide data to calculate a sample size for a trial to evaluate a wound dressing that utilises the chosen measures and frequency of measures to see whether inclusion of the measures in clinical practice can reduce the frequency of specialist clinical care. • To utilise video images to help to identify any causes of signal loss or distortion. • To investigate whether it is possible to use SIFT-MS of discarded wound dressings and GCMS of collected wound gases to measure volatile organic compounds emanating from wounds.
Trial Configuration	This feasibility study is designed as a single-centre prospective observational trial. A clinic-based evaluation of 10 patients. Participants will be seen at their usual clinical setting within the UHDB diabetic foot clinic. Participants will first receive all usual best patient care including local debridement and a temporary dressing if required. Measurements will then be taken with the OFSSWM optical probe in static position. Data will be recorded by the OFSSWM opto-electronic unit.

	Comparison will be made with conventional measurement devices. Measurements will be made within a 2-hour period during one visit for a maximum of 4 visits.
Setting	University Hospitals of Derby and Burton NHS Foundation Trust (UHDB) Secondary care diabetic foot multidisciplinary clinic.
Sample size estimate	This is a feasibility study and so is not powered for statistical testing. 10 participants will provide a sample size of up to 200 measurements for each OFSSWM parameter (humidity, NH_3, CO_2, temperature) at each visit.
Number of participants	10 participants
Eligibility criteria	• Patients with diabetes (according to WHO criteria) aged 18 years or over. • At least one full thickness ulcer below the malleolus of either foot, present for 4 weeks or more. • Ulcer located on the sole or dorsum of the foot. • No presence of wound necrosis, significant oedema or poor tissue viability that in the opinion of the investigator may at risk of deterioration with the use of OFSSWM optical probe. • At least one palpable pulse on the foot of the index limb or an ABPI $\geq$0.9. • Minimum ulcer diameter of 3 mm and maximum of 35mm. • Able to attend clinic for 4 separate visits. • eGFR >20 and not receiving dialysis. Participants would be considered ineligible if: • Planned revascularisation during the course of the study or within the 4 weeks preceding the start of the study. • An ulcer of aetiology other than diabetes. • Depth of ulcer to bone, suspected or confirmed osteomyelitis. • Severe infection of the index ulcer in accordance with IDSA criteria.

	• Active Charcot of the foot of the index ulcer. • The need for negative pressure wound therapy. • Unwilling or unable to give written informed consent. • Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, may influence the result of the trial or the participant's ability to participate in the trial. • Wound located on the toes or between the toes. • Wounds in a severe condition e.g. necrotic tissue and/or bleeding wounds.
Description of interventions	The following will be conducted in addition to standard care. The OFSSWM optical probe and sterile dressing will be placed on largest eligible wound for up to 60 minutes. The optical probe will measure humidity, temperature, NH_3, and CO_2. These will be compared with measurements from commercially available conventional sensors. Readings will be taken supine with both OFSSWM and conventional sensors. As a control, conventional measurements will also be taken in the supine position on an area intact skin.
Duration of study	Study duration: 8 months and 31 days Proposed start date: November 2022 Proposed end date: July 2023 Overall study duration per participant: up to 8 weeks
Randomisation and blinding	Participants will not be randomised or blinded.
Outcome measures	**Primary Outcomes:** Number of participants screened/consented, and reasons for not participating. Feasibility of taking measurements for each optical probe parameter from a wound. Patient feedback about the use of the optical probe. **Secondary outcomes:** humidity, NH_3, CO_2, and temperature **Safety Variables:** Adverse device events will be collected during study visits and reported to the Chief Investigator.

	Patient/user safety: Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002) and documentation will be addressed including electrical safety testing (EN 60601-1/2), design documents (ISO 13485, ISO 14155), risk assessment (ISO 14971), and biocompatibility (ISO 10993 series).
Statistical methods	All feasibility outcomes will be reported as rates and summarised into frequency tables. The optical probe parameters will be compared between the intervention and conventional devices using Paired T-Test, and presented graphically using Bland-Altman plots.

ABBREVIATIONS

ABPI	Ankle brachial pressure index
ADE	Adverse Device Effect
AE	Adverse Event
BP	Blood pressure
CHD	Coronary heart disease
CI	Chief Investigator overall
CRF	Case Report Form
CVD	Cardiovascular disease
DAP	Data Analysis Plan
DFU	Diabetic Foot Ulcer
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOT	End of Trial
GCP	Good Clinical Practice
ICF	Informed Consent Form
IDSA	Infectious Diseases Society of America
ITT	Intention to Treat
MHRA	Medicines and Healthcare Products Regulatory Agency
NAMSA	North American Science Associates
NHS	National Health Service
OFS	Optical fibre sensor
OFSSWM	Optical Fibre Sensing System for Wound Monitoring
PAD	Peripheral arterial disease
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development Department
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SIFT-MS	Selected ion flow tube mass spectrometry

TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHDB	University Hospitals of Derby and Burton NHS Foundation Trust
UoN	University of Nottingham
VAS	Visual Analogue Scale
WHO	World Health Organisation
WUWHS	World Union of Wound Healing Societies

TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Background

Chronic wounds are a significant burden to healthcare providers worldwide, with the annual cost of treatment in the UK is ~4% of the entire NHS budget [1]. Among chronic wounds, diabetic foot ulcers (DFUs) is a particular group which currently accounts for almost £1 billion each year – almost 1% of the total NHS cost [2]. The bulk of these costs are made up of NHS appointments and hospital admissions for DFUs which deteriorate.

NICE guidelines for DFU wound dressings are based on a paucity of evidence and states choice of wound dressings should take into account the clinical assessment of the wound and use the lowest cost appropriate to the clinical circumstances [3]. Smart dressings for use in chronic wounds is an emerging field and the majority under development focus on monitoring a single parameter. In the complex wound micro-environment, several biomarkers are associated with healing [4] and it is unlikely that approaches based on monitoring a single parameter will be sufficient.

This study is focused on an Optical Fibre Sensing System for Wound Monitoring (OFSSWM), which aims to monitor multiple parameters and use technology which could have a significant impact on wound care costs and patient quality of life. Introducing remote monitoring of wound status via optical fibre sensing will notify a patient and clinician when the wound is in an adverse state, either wound healing is not progressing or the wound is infected. This will enable clinical interventions to take place promptly but only when required, thus improving wound care and reducing the number of NHS appointments. For example, if monitoring indicates that wound healing is progressing well then this will reduce the need for specialist review and can reduce the frequency of dressing changes. If the wound status deteriorates rapidly, e.g. due to infection, then this will trigger urgent specialist review. There is evidence that early expert assessment of DFUs leads to improved outcome, with reduced hospital admissions and amputations [5].

There is a great clinical need to focus research on treatment of DFUs as over 80% of people with diabetes who lose a leg initially present with a foot ulcer [6]. The burden is increasing with the increasing prevalence of Type 2 diabetes and ~100 leg amputations are performed each week in the UK. The evidence of wide geographical variation suggests that many are likely to have been avoidable [7]. Better wound monitoring has the potential to provide earlier intervention and reduce amputations.

The proposed approach will monitor 4 key parameters on inexpensive optical fibre sensors (OFS) (i.e. the OFSSWM optical probe) incorporated onto a sterile wound dressing (provided as part of the OFSSWM), which sits on the wound bed and acts as a sterile barrier between the wound and optical probe. The parameters have been selected with the aim of striking a balance between evidence in the scientific literature and likelihood of successful implementation within a dressing. Clinical studies will investigate whether the number of sensors can be reduced which would simplify the instrumentation required, ideally towards sensors which do not involve contact with the skin or exudate (CO_2, NH_3, temperature, humidity). Scientific literature has more published on pH but this involves contact of the sensor with wound exudate which is susceptible to biofouling. Monitoring of gases is less well documented but is advantageous as the sensor can be situated away from exudate.

There is an interdependence between some parameters e.g. pH and NH_3 are indicative of infection [8], increased partial pressure of CO_2 leads to a decrease in pH and lowers haemoglobin's affinity for oxygen, increasing the delivery of oxygen to the wound [9].

The final device will comprise the disposable optical probe which will be periodically connected to a standalone reusable opto-electronic unit to monitor wound status parameters on a (likely) daily basis. Ultimately, we envisage a machine learning algorithm such as a support vector machine or artificial neural network (e.g. [10]) being trained to recognise the signals from the multiple sensors that correspond to wound status. An appropriate scale (e.g. numeric or colour) will then be used to indicate wound status. For example:

1) Healing well, no action needed (green).

2) Healing slower than anticipated but not infected, change dressing, inspect wound and check pressure relief at next convenient opportunity (amber).

3) Wound in early stages of infection, return to clinic (red).

For example, academic literature suggests that wounds that are healing well are associated with pH<7.6, absence of ammonia, increasing CO_2 levels, low blood oxygen saturation in the peri-wound region, a moist environment and stable temperature. Data is studies by [11] and [12] show typical values from the literature along with the current resolution of our sensors. All of these demonstrate that the measurement approach is feasible if the laboratory performance of the sensors can be matched in vivo. The proposed OFSSWM has been tested under laboratory conditions thus greatly reducing risk to patients at this stage of testing. Biocompatibility testing of the optical probe conducted via an independent test organisation North American Science Associates (NAMSA) has assessed biological risk as low (please see document 'QMS-OFS-TF-16 Biocompatibility Report' for more information).

This is a feasibility study and so is not powered for statistical testing. 10 participants will provide a sample size of up to 200 measurements for each OFSSWM parameter (humidity, NH_3, CO_2, temperature) at each visit.

Benefits

Monitoring wound status remotely via optical fibre sensing will notify the patient and clinician when the wound is in adverse state, either wound healing is not progressing or the wound is infected. This will enable clinical interventions to take place promptly but only when required, thus improving wound care and reducing the number of NHS appointments. For example, if monitoring indicates that wound healing is progressing well then this will reduce the need for specialist review and can reduce the frequency of dressing changes. On the other hand, if the wound status deteriorates rapidly, e.g. due to infection, then this will trigger urgent specialist review, which will lead to improved outcome, e.g., reduced admissions and amputations.

Cost savings can be made through monitoring of wound status. Stratification of different wound categories (e.g. identifying wounds that are difficult to heal) will make an even more compelling case

for the technology. Better wound care will result in reduced time to healing and therefore reduction in costs across all areas of diabetic foot ulcer management simply because patients will spend less time being treated.

Although there will be a higher unit cost associated with the disposable sensorised dressing and reusable electronic unit (~£4 - £9 per use compared to £2 average for current dressings), we believe that this will be offset by fewer dressing changes and reduced time to healing. There will also be additional savings due to an anticipated reduction in hospital, GP and home visits and reduced number of amputations. The device will indicate the most appropriate time to change the dressing and whether intervention is required (e.g. due to infection). A 10% reduction in costs associated with visits and admissions categories would provide a £300m annual saving to the NHS. The final product would initially concentrate on those most at risk of a non-healing wound before applying the technology to a wider population of those with chronic wounds.

DETAILS OF INVESTIGATIONAL MEDICAL DEVICE

Device Description

A) The manufacturer of the device, its model or type number and CE mark status

Manufactured by University of Nottingham, Faculty of Engineering. The device has been tested for safety Patient/user safety (Medical Devices Directive 2002 and its 2020 Amendment) and documentation is addressed including electrical safety testing (EN 60601-1/2), design documents (ISO 13485, ISO 14155), risk assessment (ISO 14971), and biocompatibility (ISO 10993 series).

B) Purpose of the device, clinical indications and contraindications for use

The OFSSWM is comprised of 3 main components: an optical probe, a sterile dressing, and an opto-electronic unit. The optical probe and the sterile dressing are single-use elements, whereas the opto-electronic unit can be reused. The opto-electronic unit is intended to be placed at least 2m apart from the patient, whereas the optical probe (connected to the opto-electronic unit via a fibre optic cable and an optical adapter) will be placed on a single-use sterile dressing (including a biocompatible PTFE membrane), which provides a sterile barrier between the wound bed and the optical probe, as shown in Figure 1. The sterile dressing and the optical probe will then be held in place using clinically available materials (e.g., medical tape and/or bandage), as appropriate to the wound being investigated. A specified mains adapter is used to power the opto-electronic unit.

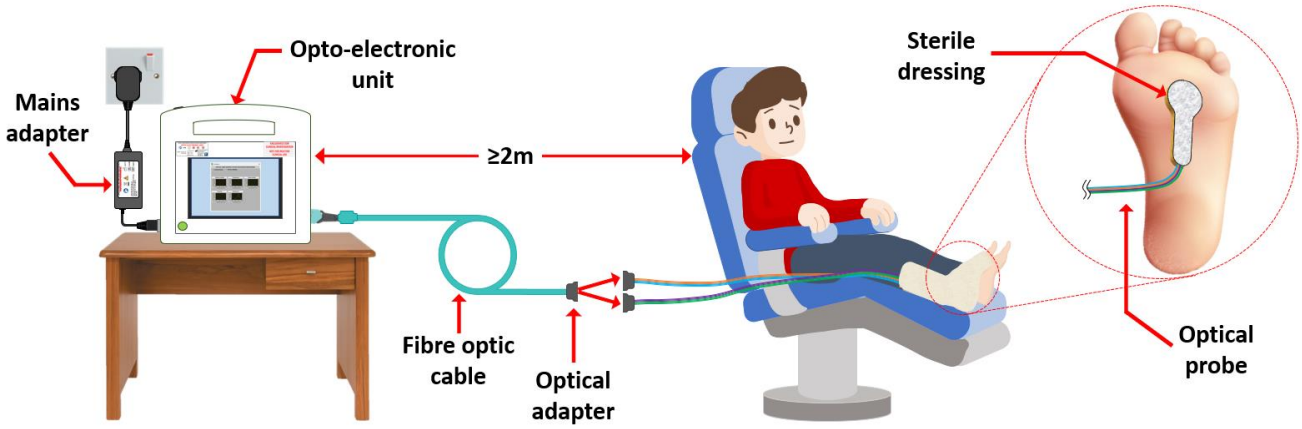

Figure 1. Optical Fibre Sensing System for Wound Monitoring (OFSSWM) overview.

Clinical Indications

The OFSSWM is intended to monitor biomarkers associated with wound healing namely: relative humidity; temperature; carbon dioxide (CO_2); and ammonia (NH_3). It non-invasively interacts with the external wound micro-environment by placing the device optical probe on a sterile barrier dressing (provided as part of the OFSSWM), which sits on the wound bed. The information regarding the measurements of biomarkers is displayed by the device opto-electronic unit via software for interpretation by members of the engineering team.

The OFSSWM is intended to be used by the clinical team with support from members of the engineering team to monitor patients with DFUs as part of a clinical investigation. The ultimate aim of the device is to indicate whether wound healing is progressing satisfactorily or whether an intervention is required (e.g., due to infection). However, **the purpose of the clinical investigation is to simply record optical data (potentially leading to biomarker values) from people with DFUs in order to ascertain device performance and safety. At no time will the patient normal care pathway be modified as a result of the optical data collected from this experimental device.**

Contra-indications

The operation of the opto-electronic unit will be performed by a member of the engineering team, whereas the placement of the optical probe and the sterile dressing (provided as part of the OFSSWM) will be made by a member of the clinical team. These will work as a team which will reduce risk of contra-indications. However, the following will be considered throughout a study visit:

- The device is not to be used if any part of it (including the optical probe packaging and the sterile dressing packaging) is damaged or dirty.
- The device is NOT intended to be operated by the patient.
- The optical probe and the sterile barrier dressing are not to be re-used. After use, they will be disposed of as per the Clinical Waste management process of the University Hospitals of Derby and Burton NHS Foundation Trust.

- The OFSSWM is NOT intended for routine clinical use.

DEVICE PRINCIPLE OF OPERATION

The principle of operation of the OFSSWM is based on the interaction of light launched into the sensing element, i.e. the optical probe with the surrounding medium (wound area) and the analysis of the reflected light by the opto-electronic unit to provide a value of 4 key parameters associated with wound healing, as described in Table 1:

Table 1. Biomarkers measured by the Optical Fibre Sensing System for Wound Monitoring.

Biomarker	Abbreviation	Units
Relative Humidity	RH%	%
Temperature	T	°C
Carbon dioxide	pCO_2	ppm
Ammonia	NH_3	ppm

OPTICAL PROBE

The optical probe is a single-use element. Figure 2 shows an overview of the optical probe. At one end, it has two optical connectors for connection to the opto-electronic unit via an optical adapter for signal analysis. At the other end, the optical probe has an array of optical fibres coated with sensitive films on its tip, i.e., OFSs to detect the parameters described in Table 1. The OFSs are enclosed within a set of double-side medical tape (Double coated “2-in-One” medical silicone/acrylic tape, 3M Ltd., UK) and micropore tape (Hypafix, BSN Medical Ltd., UK). The OFSs are intended to sit on top of a sterile barrier dressing, which is provided as part of the OFSSWM, as described in the document ‘QMS-OFS-TF-10 Instructions For Use’. The OFSs have been assessed as low risk during biocompatibility assessment by an independent test house (please see ‘QMS-OFS-TF-16 Biocompatibility Report’).

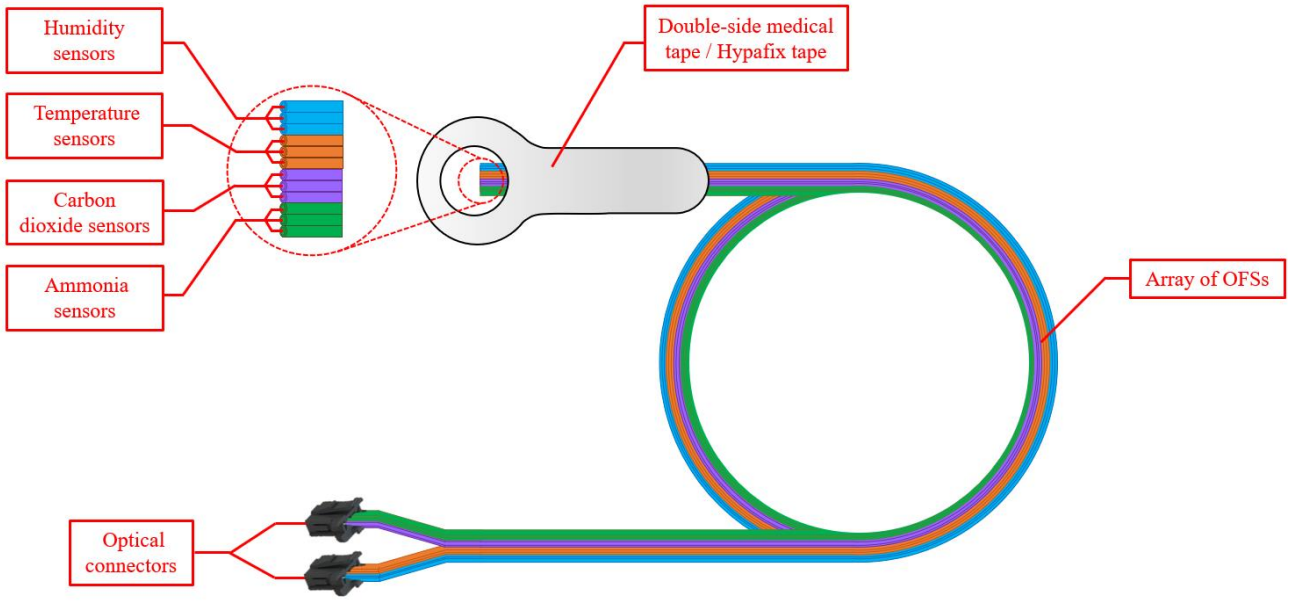

Figure 2. Optical probe detailed view.

STERILE DRESSING

Figure 3 illustrates the sterile dressing intended to be used as a barrier between the wound bed and the optical probe. It is based on an approved foam wound dressing (Biatain® non-adhesive foam dressing, Coloplast Ltd., UK), double-side medical tape (Double coated "2-in-One" medical silicone/acrylic tape, 3M Ltd., UK), and a PTFE membrane (FlontexTM 100 PTFE filter membrane, Polyflon Technology Ltd., UK). Further information is provided in supporting document 'QMS-OFS-TF-16 Biocompatibility Report'.

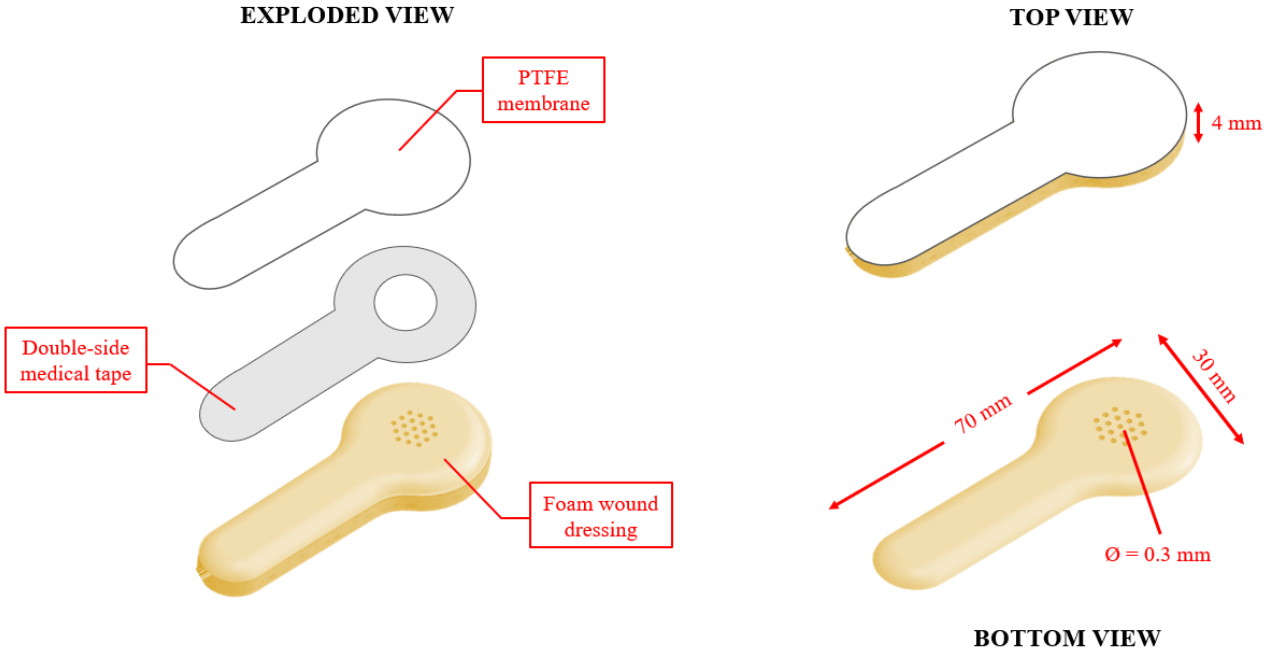

Figure 3. Sterile barrier dressing detailed view.

Figure 3 (left) shows an exploded view for the assembly of the sterile dressing. The foam wound dressing (bottom layer) is intended to be in contact with the wound bed. It has a set of holes to allow gases to travel through the sterile dressing. The PTFE membrane (top layer) provides an impermeable surface to place the optical probe and protect it in the event of excessive wound exudate.

The assembly, individual packaging, and sterilisation of the sterile dressing was subcontracted to Medical Device Management (MDM) Ltd., UK., in a clean room within their facilities. The sterile dressing undergoes sterilisation by autoclave method. Please see 'QMS-OFS-TF-14 Sterilisation Report' for further details regarding the sterilisation process and validation.

OPTICAL PROBE PRINCIPLE OF OPERATION

The optical probe sensing section (i.e., the OFSs) is intended to be adhered on the sterile dressing top layer (PTFE membrane). On the other side, the optical probe is intended to be connected to the opto-electronic unit via an optical adapter and a 2m fibre optic cable, as shown in Figure 1. The document 'QMS-OFS-TF-10 Instructions For Use' provides more information for the optical probe and sterile dressing application on the wound area. The opto-electronic unit launches light down the fibre optic cable and into the optical probe. Light travels to the optical probe sensing section, where the interaction with the external wound micro-environment will reflect light back to the opto-electronic unit. Figure 4 illustrates the principle of operation for one of the OFSs on the optical probe. The light intensity returning to the detector in the opto-electronic unit represents the measured parameter.

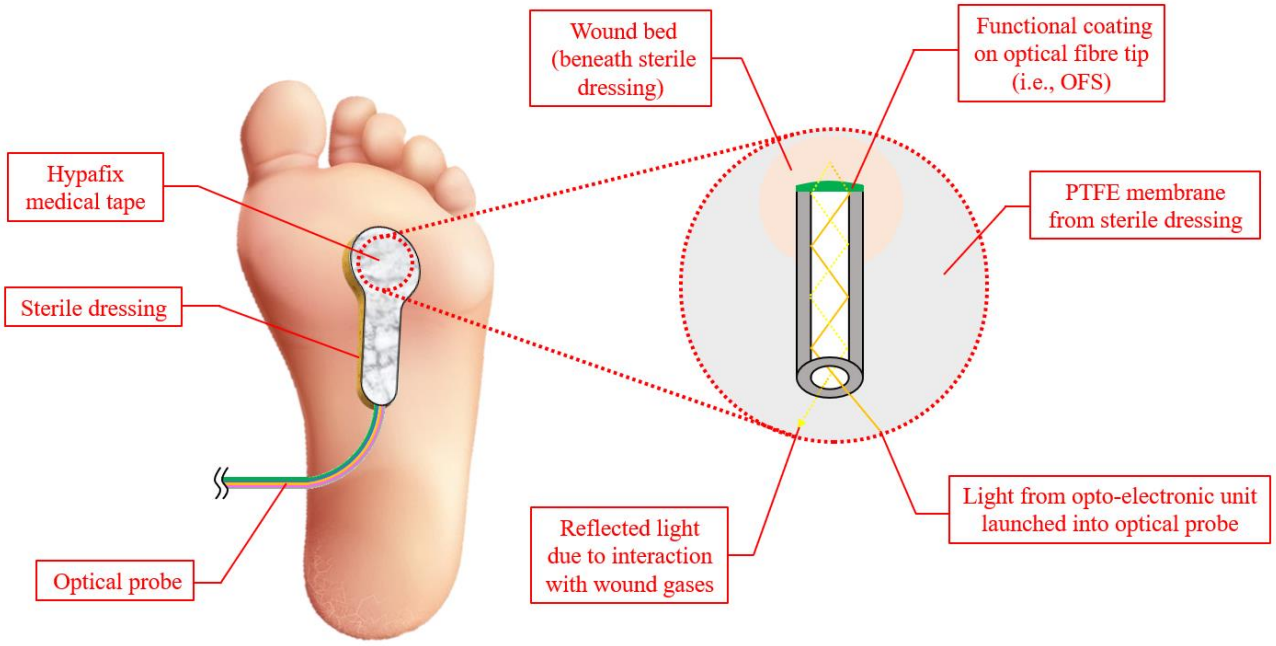

Figure 4. Optical probe principle of operation.

OPTO-ELECTRONIC UNIT

The opto-electronic unit can be operated once it is connected to the mains adapter and this is plugged into the mains socket. The opto-electronic unit is compliant with medical device regulations after testing and assessment by the Clinical Engineering department at Nottingham University Hospitals NHS Trust (please see the documents 'QMS-OFS-TF-07A Electrical Safety' and 'QMS-OFS-TF-12 Test and pre-Clinical Data' for more information). An indicator light at the front of the opto-electronic unit turns on when the device is ready for use. The opto-electronic unit principle of operation is divided into a sequence of four actions, as illustrated in Figure 5 and described in Table 2. The optical probe shall be connected to the opto-electronic unit (via a fibre optic cable and an optical adapter) to perform its intended use. Figure 6 shows the OFSSWM block diagram to describe the device principle of operation. Further detailed information is provided in the document 'QMS-OFS-TF-07 Device Details'.

Figure 5. Diagram of opto-electronic unit principle of operation.

Table 2. Opto-electronic unit principle of operation.

Action	Description
1. Illumination	The opto-electronic unit internal light source launches light (wavelength range: 360nm – 2.4µm) into the optical probe.
2. Detection	The optical probe sensitive film changes optical properties due to interaction with the external wound micro-environment. These changes can be observed in the reflected light (optical signal) which is guided to the internal detector (spectrometer) in the opto-electronic unit.
3. Processing	The optical signal is digitised and processed by the opto-electronic unit internal micro-controller and software following a calibration curve from each sensor.
4. Display	The measured values from each biomarker (Table 1) are shown in the opto-electronic unit display for viewing by a member of the engineering team only.

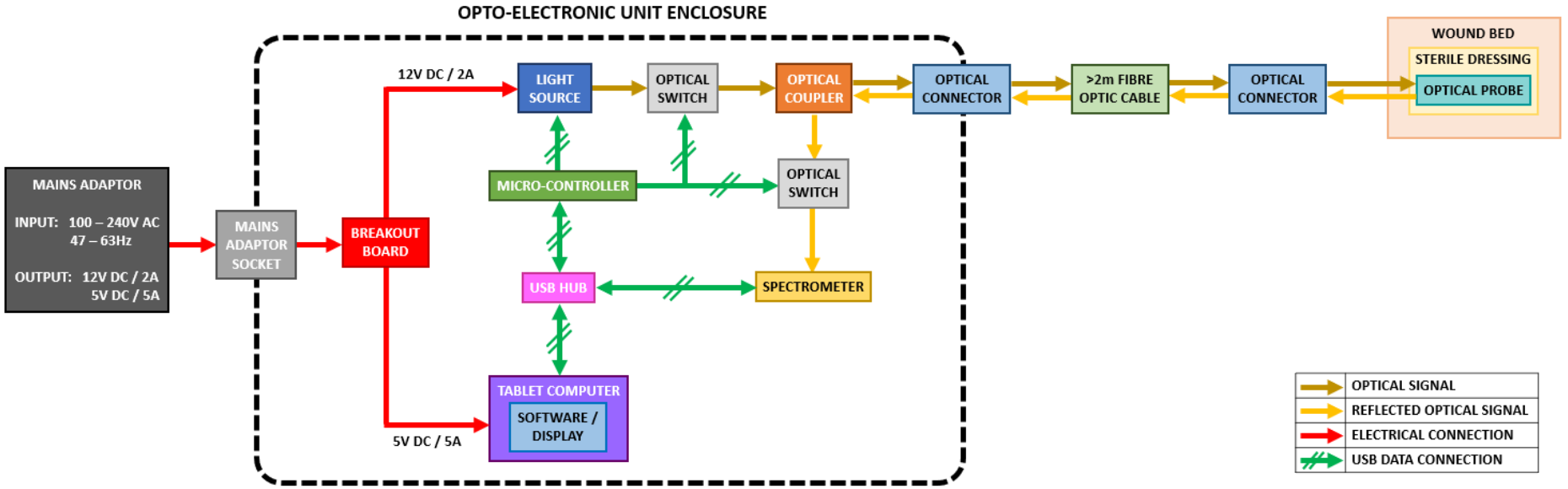

Figure 6. Optical Fibre Sensing System for Wound Monitoring block diagram.

PACKAGING AND LABELLING

Labels

The manufacturers label identifies the optical probe (Figure 7), the sterile dressing (Figure 8), the opto-electronic unit (Figure 9), and the opto-electronic unit mains adapter (Figure 10) of the OFSSWM. Information regarding the symbols and additional markings applied to these elements is provided in the document 'QMS-OFS-TF-11 Device Labels'.

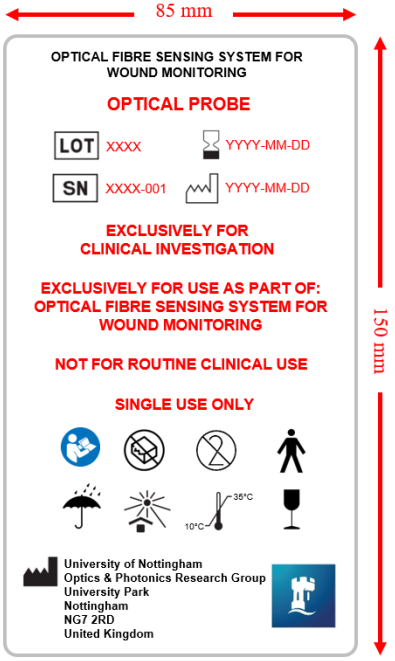

Figure 7. Optical probe manufacturer's label.

Figure 8. Sterile dressing manufacturer's label.

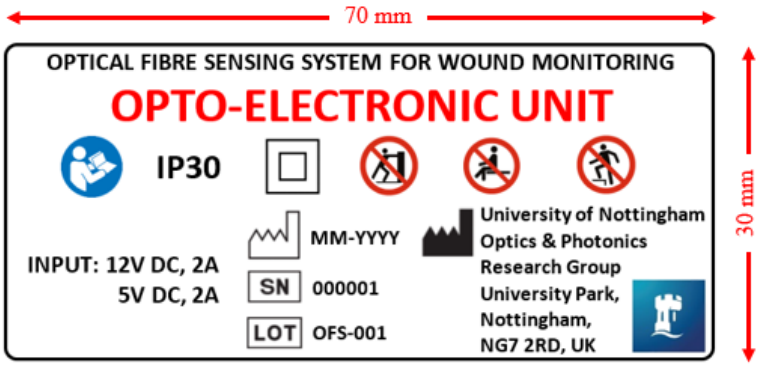

Figure 9. Opto-electronic unit manufacturer's label.

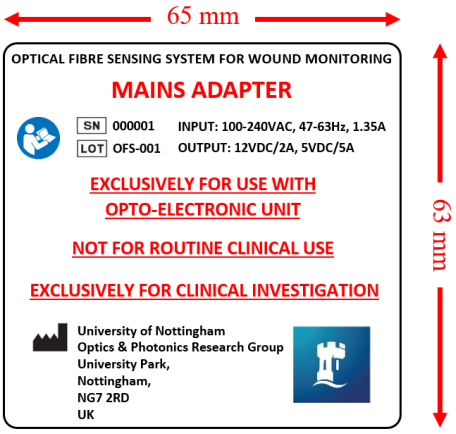

Figure 10. Opto-electronic unit mains adapter label to identify it as part of the OFSSWM.

An additional label (Figure 11) is attached to the opto-electronic unit enclosure. This label includes a highlighted statement regarding the device purpose for research only and not for routine clinical use.

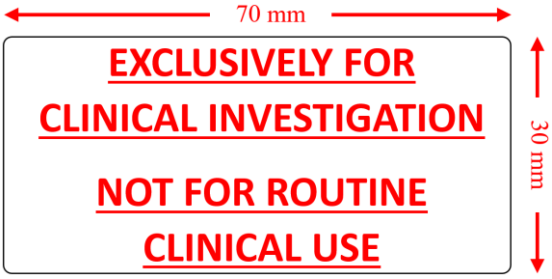

Figure 11. Label to indicate the use of the opto-electronic unit exclusively for a clinical investigation.

The safety label and markings for the optical probe and the sterile dressing are applied to their individual packaging, as shown in Figure 12 and Figure 13, respectively. The opto-electronic unit labels are applied on the front face of its enclosure (Figure 14), so that it is clearly visible. This helps to mitigate the risk that the opto-electronic unit will inadvertently be used for routine clinical use, as explained in the document 'QMS-OFS-TF-09 Risk Management'. The opto-electronic unit mains adapter label is located on its top face, as illustrated in Figure 15.

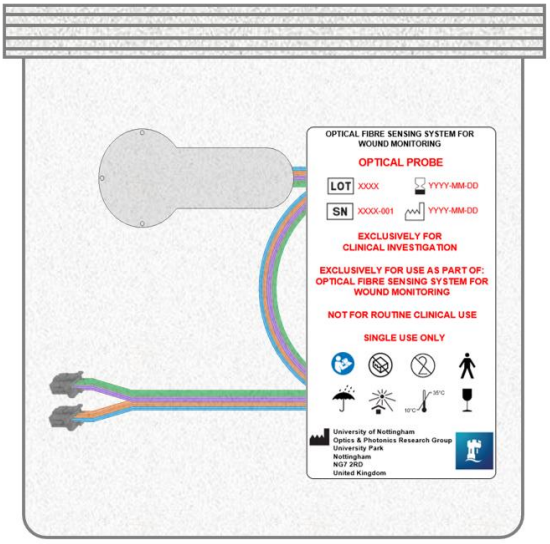

Figure 12. Optical probe label and markings affixed to its individual packaging.

Figure 13. Markings and labelling for the sterile dressing affixed to its individual packaging.

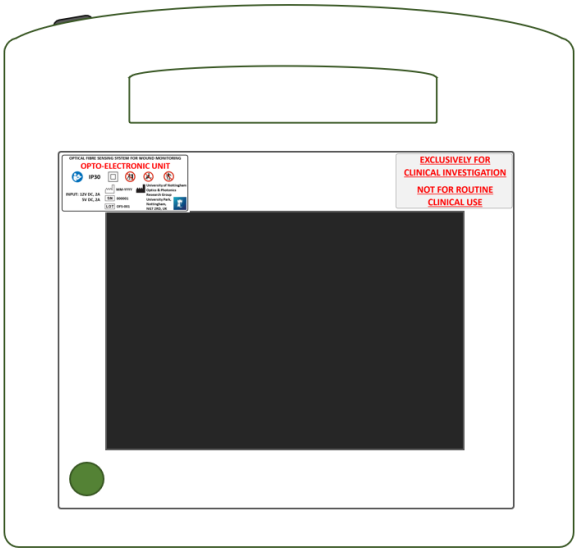

Figure 14. Opto-electronic unit label position.

Figure 15. Opto-electronic unit mains adapter label position.

Storage, supply and return

There are no special storage conditions for the device. When not in use, it will be held in a secure locked cabinet at UHDB with access only by the Chief Investigator, podiatrist (member of the clinical team), and the Head of Clinical Engineering. The devices will be kept separately to other supplies and labelled accordingly (with the trial labels as described above). Surplus or unused optical probes, sterile dressings, and the opto-electronic unit with its mains adapter will be returned to the University of Nottingham laboratories.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To explore the use of multi-parameter optical fibre sensors in the management of diabetic foot ulcers (DFUs).

PRIMARY OBJECTIVE

To explore the feasibility of using the Optical Fibre Sensing System for Wound Monitoring (OFSSWM) in a clinical environment.

SECONDARY OBJECTIVES

1. To compare the OFSSWM optical probe to conventional measurement devices. The parameters to be assessed are: humidity, NH_3, CO_2, and temperature.

2. To provide data to calculate a sample size for a trial to evaluate a wound dressing that utilises the chosen measures and frequency of measures to see whether inclusion of the measures in clinical practice can reduce the frequency of specialist clinical care.

3. To utilise video images to help to identify any causes of signal loss or distortion.

4. To investigate whether it is possible to use SIFT-MS of discarded wound dressings and GCMS of collected wound gases to measure volatile organic compounds emanating from wounds.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

This OFSSWM feasibility study aims to evaluate the use of multi-parameter optical fibre sensors in the management of DFU. A single-centre prospective observational trial, recruiting patients from University Hospitals of Derby and Burton NHS Foundation Trust (UHDB).

Primary endpoint

The following feasibility outcomes will be the primary endpoints:

1. Number of participants screened/consented, and reasons for not participating.

2. Non-completion rate and reasons.

3. Feasibility of taking measurements for each optical probe parameter (Table 1) from a wound. To assess: the best optical probe position with regard to the surface of the wound, number of failures to get any readings per parameter, reasons for signals becoming distorted.

4. To investigate whether GCMS of discarded wound dressings to measure parameters as above is possible.

Secondary endpoints/ outcome measures

- Wound size measured as per normal clinical care with Silhouette wound assessment camera (Entec Health Ltd).
- Incidence of secondary infection.

- Pain in the area of the ulcer as assessed by patient completed 100mm Visual Analogue Scale (VAS).

Safety endpoints

Adverse events (AE's) including major and minor amputations and hospitalisation will be recorded in an adverse event log and reported to the Chief Investigator. Safety variables and device related AEs will be reported during the study, discontinuations will be assessed by the Chief Investigator due to AEs, results of physical examinations, vital signs (pulse rate, BP), and special investigations such as ECGs, clinical laboratory data and results of scans.

Stopping rules and discontinuation

The stopping rules or discontinuation criteria for individual participants, for parts of the trial or the entire trial involves:

- Deterioration of the wound that in the opinion of the Investigator may be caused by the OFSSWM.

- Pain or discomfort from the OFSSWM.

TRIAL MANAGEMENT

A central coordinating centre will be responsible for the day to day running of the study with the trial manager (Blackshaw) reporting to a Trial Management Group (Game, Gray, Fakis, Morgan); and there will be a Data Monitoring Committee. The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator. The Trial Management group will meet to discuss the conduct and running of the trial a minimum of 12 weekly.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: The duration of each participant's involvement with the study will be up to 8 weeks. Participants will be observed fortnightly for 4 visits.

The baseline visit will last up to 2.5 hours with each visit after this (visit 2-4) lasting around 2 hours.

End of the Trial

The end of the trial and the last study visit of the last recruited participant will be in June 2023. The end of the study will be the last visit for the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Patients who fulfil the inclusion criteria and have DFUs being treated at the specialist diabetic foot clinic at the University Hospitals of Derby and Burton NHS Foundation Trust, (Royal Derby Hospitals and London Road Community Hospitals sites) will be invited to participate by their usual clinical carers

at an existing clinic visit. The clinical notes of patients booked to attend clinic will be screened before attendance at clinic to see if they fulfil the inclusion criteria. This will be done by members of the clinical team caring for them. If the patient fulfils the criteria they will be asked if they might be interested by the clinical team and, if so, a patient information sheet will be given to the patient and they will be approached again at their next clinic visit or by phone by a member of the clinical team to discuss. If they remain interested they will then be booked into a research visit and informed consent taken at that visit. Patients will be given at least 24 hours to consider taking part in the trial before signing a consent form.

It will be explained to potential participants that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

Patients will be eligible for inclusion only if ALL of the following criteria apply:

- Ulcer located on the sole or dorsum of the foot.
- At least one full thickness ulcer below the malleolus of either foot, present for 4 weeks or more.
- Patients with diabetes (according to WHO criteria) aged 18 years or over.
- No presence of wound necrosis, significant oedema or poor tissue viability that in the opinion of the investigator may at risk of deterioration with the use of OFSSWM optical probe.
- At least one palpable pulse on the foot of the index limb or an ABPI $\geq$0.9.
- Minimum ulcer diameter of 3 mm and a maximum diameter at any point of 25 mm.
- Able to attend clinic for 4 fortnightly visits.
- eGFR >20 and not receiving dialysis.

Exclusion criteria

- Planned revascularisation during the course of the study or within the 4 weeks preceding the start of the study.
- An ulcer of aetiology other than diabetes.
- Depth of ulcer to bone, suspected or confirmed osteomyelitis.

- Severe infection of the index ulcer in accordance with IDSA criteria.
- Active Charcot of the foot of the index ulcer.
- The need for negative pressure wound therapy.
- Unwilling or unable to give written informed consent.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, may influence the result of the trial or the participant's ability to participate in the trial.
- Wound located on the toes or between the toes.
- Wounds in a severe condition e.g. necrotic tissue and/or bleeding wounds.

Expected duration of participant participation

Study participants will be part of the study for 4 separate visits and will attend their usual UHDB foot clinic setting.

Participant Withdrawal

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- An adverse event which requires discontinuation of the trial application or results in inability to continue to comply with trial procedures.
- Loss of capacity to consent.

The only reason a participant may be withdrawn from study follow-up is in the event of withdrawal of consent, loss of capacity to consent or an adverse event which in the opinion of the Investigator was related to the study. Participants that are withdrawn from the study will be replaced by eligible participants.

If a patient withdraws consent or loses capacity such that they are unable to consent to continue in the study then data collected up until that point will still be used in the analysis. Reason for not completing the study will also be collected. Further information will not be collected from patients who have withdrawn from the study.

Informed consent

Informed consent must be obtained before any trial-related procedures are undertaken. In addition to receiving the patient information sheet the researchers will fully explain the background and aims of

the study, and explain what will happen if they decide to participate in the study and what they can expect if they do not participate before written consent is taken.

The participant must personally sign and date the latest approved version of the informed consent form before any trial specific procedures are performed.

Written and verbal versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the trial; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. This will include information regarding the theoretical risks of the OFSSWM application. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information (at least 24 hours), and the opportunity to question the Investigator, or other independent parties to decide whether they will participate in the trial. Written informed consent will then be obtained at the start of the baseline visit by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be a suitable qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed informed consent will be given to the participants.

The original signed form will be retained in the TMF. In accordance with the Sponsor's standard operating procedure a copy of the original signed form will be filed in the patient's medical notes.

A screening log will be maintained at the clinical site detailing the number of patients approached about the study and the number agreeing to participate. A master copy of the screening log can be found in the study investigative site file.

The following will be recorded on the screening log:

- Hospital number.
- Sex.
- Age.
- Inclusion.
- Study number if included, or reason for non-inclusion if not.

TRIAL / STUDY TREATMENT AND REGIMEN

Baseline visit

Patients must give written informed consent before any trial specific screening investigations may be carried out. After written consent, the baseline assessments as below should be conducted and recorded in the appropriate CRF.

- Demographics: Age, sex and type of diabetes.
- Medical History: Details of any history of, cardiovascular disease (CVD), coronary heart disease (CHD) or renal disease.
- Concomitant Medication: All over-the counter or prescription medication will be recorded.
- Laboratory Tests: eGFR and HbA1c – only if not done as part of usual care within last 12 months.
- If the patient has more than one foot ulcer, one will be designated as the index ulcer. This will be the clinically most significant and will usually be the largest eligible ulcer.
- Assessment of Pain associated with their DFU (100 mm VAS).
- Wound dressing removed and placed into plastic bag for SIFT-MS.
- Wound status: Site of ulcer, area, depth, extent of surface slough, pain (VAS).
- Assessment of ulcer infection by IDSA criteria (0 = none, 1 = mild (limited to skin and subcutaneous tissues and with inflammation limited to within 2cm of wound margin), 2 = moderate (deeper and/or with more extensive inflammation) and 3 = severe (with systemic symptoms and signs)).
- Assessment of peripheral pulses by palpation.
- Assessment of neuropathy using 10g monofilament.
- Ankle brachial pressure index (ABPI) measurement.
- Silhouette digital image and measurement of index ulcer as per usual care.
- Initial application of OFSSWM – measurement in supine position on the wound.
- Conventional measurement devices (sampling sensors for CO_2, NH_3, temperature, humidity and pH probe) – measurement in the supine position only, on the wound. Collection of gases via a sorption tube for later GCMS analysis at the Open University.

- Video recording of wound/foot during the time the OFSSWM and conventional measurement devices are in place to allow data to be synchronised with any time the signals become distorted and establish any reasons why.

- Following removal of the conventional measurement devices from the wound bed, the patient will have their wound dressed in the usual way.

- Conventional measurement devices (sampling sensors for CO_2, NH_3, temperature, humidity). Collection of gases via a sorption tube for later GCMS analysis at the Open University – measurement in the supine position only, on the intact foot skin (control measurements).

For further instructions on local SOPs/work instructions for the conduct of these assessments please refer to the document 'QMS-OFS-TF-10 Instructions For Use'.

The conventional devices, the OFSSWM optical probe, and the sterile dressing will be applied by a research Podiatrist (member of the clinical team). A member of the engineering team will take measurements with the opto-electronic unit from the OFSSWM and conventional measurement devices.

OFSSWM measurement on wound bed:

1) Initial removal of dressing and capturing in a plastic bag to measure wound gases via SIFT-MS (dressing in place for at least 12 hours prior to removal). Dressing will be stored at -70 °C at site prior to shipping (via tracked courier delivery) on dry ice to Prof Claire Turner, Brunel University. A swab will be taken from the wound and a measurement of pH taken with a probe (once measured, the swab will be destroyed as clinical waste). Placement of a sterile barrier dressing (provided as part of the OFSSWM) and the OFSSWM optical probe on the wound bed by the research Podiatrist (member of the clinical team).

2) OFSSWM measurement procedure in supine position on the wound bed by the member of the engineering team. A video recording will be taken whilst the OFSSWM optical probe is in place to synchronise the video to the signal which would help the member of the engineering team to identify reasons for signals becoming distorted during post-processing and analysis. Video recordings will only be made of the wound bed and any identifying marks e.g. tattoo, will be manually removed from the video capture using software.

3) Removal of OFSSWM optical probe and sterile dressing.

Conventional measurement devices on wound bed:

4) A sterile dressing (provided by the engineering team) will be placed on the wound bed by the research Podiatrist (member of the clinical team). The chamber for gas collection will be placed on the sterile dressing by the research Podiatrist (member of the clinical team).

5) Measurement of the wound bed in supine position only. A video recording will be taken whilst the gas chamber is in place to synchronise the video to the signal which would help the member of the engineering team to identify reasons for signals becoming distorted during post-processing and analysis. Video recordings will only be made of the wound be and any identifying marks e.g. tattoo, will be manually removed from the video capture using software.

6) Removal of chamber for gas collection and sterile dressing after completion of measurements.

7) Wound dressed as usual way by Podiatrist (member of the clinical team).

Conventional measurement devices on intact foot skin:

8) A sterile dressing (provided by the engineering team) will be placed on the intact foot skin by the research Podiatrist (member of the clinical team). The chamber for gas collection will be placed on the sterile dressing by the research Podiatrist (member of the clinical team).

9) Measurement of the intact foot skin in supine position only. A video recording will be taken whilst the gas chamber is in place to synchronise the video to the signal which would help the member of the engineering team to identify reasons for signals becoming distorted during post-processing and analysis. Video recordings will only be made of the wound be and any identifying marks e.g. tattoo, will be manually removed from the video capture using software.

10) Removal of chamber for gas collection and sterile dressing after completion of measurements.

All removed dressings will be destroyed in accordance with the Human Tissue Act.

Conventional CE-marked measurement devices (described in Table 3) will be used within their intended indication to measure CO_2, NH_3, temperature, humidity, and pH of the wound micro-environment. A pH probe will measure the pH of wound exudate obtained from a swab (Figure 16). A sterile dressing will be placed as a barrier between the gas chamber and the wound bed (Figure 17). Temperature and humidity measurements will be obtained from a single sensor placed within the chamber that sits over the sterile dressing, as shown in Figure 18. CO_2 and NH_3 will be measured by extracting gases from the headspace above the sterile dressing on the wound bed flowing them over conventional sensors, as illustrated in Figure 19. Wound gases will be collected by a sorption tube within the conventional measurement devices set-up for further analysis of volatile organic compounds outside the clinic (at the Open University). The conventional measurement devices are contained within a plastic enclosure, as shown in Figure 20, and it will be carried by members of the engineering team. A safety label placed on the conventional measurement devices enclosure indicates that it is exclusively for clinical investigation and not for routine clinical use.

Table 3. Conventional devices for biomarker measurements on wounds.

Parameter	Name	Ref. number	Sampling rate	Detection range	Resolution	Supplier
Humidity	iButton Hygrocron Humidity/Temperature data logger	DS1923	1s – 273h	0 – 100%RH	0.6%RH	Maxim Integrated
pH	Handheld pH meter	PHH-37	1s	0 – 14 pH	0.01±0.03	Omega Engineering
Carbon dioxide	CO_2 datalogger	K-33 BLG	2s	0 – 300,000 ppm	±0.2% CO_2	CO2meter.com
Ammonia	Honeywell 4NH3-100 Ammonia sensor	CLE-1012-401	60s response time	0 – 100 ppm	0.5 ppm	Winsensors
Temperature	iButton Hygrocron Humidity/Temperature data logger	DS1923	1s – 273h	-20°C - +85°C	0.5°C	Maxim Integrated
Volatile Organic Compounds	Sorption tube	C3-AAXX-5266	200 mL/min	-----	-----	Markes International

Figure 16. Conventional device for pH measurements from swab taken from the wound.

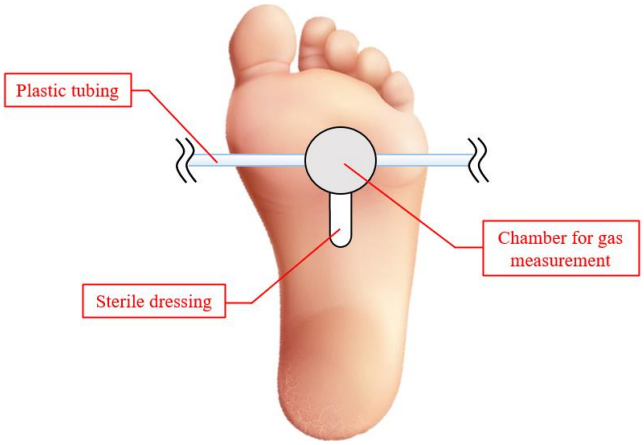

Figure 17. Placement of chamber for gas measurement from the wound bed.

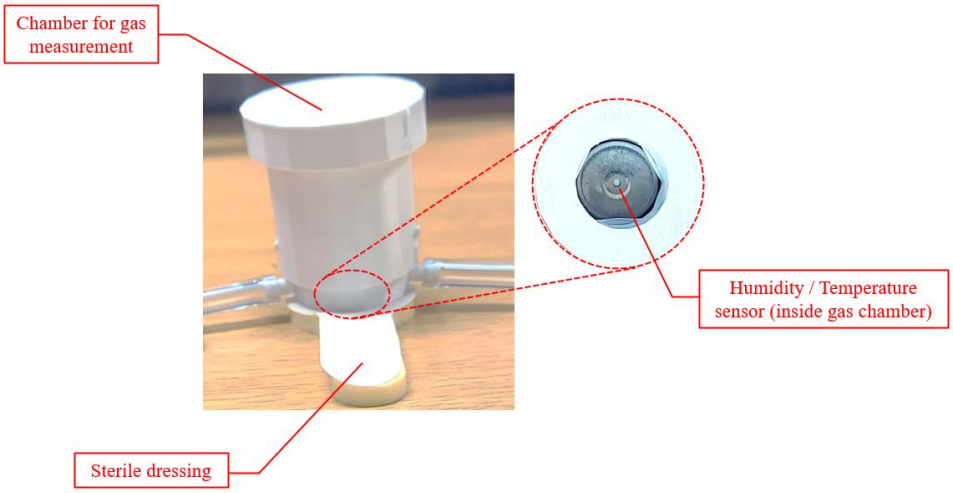

Figure 18. Chamber for gas measurements including temperature and relative humidity sensor.

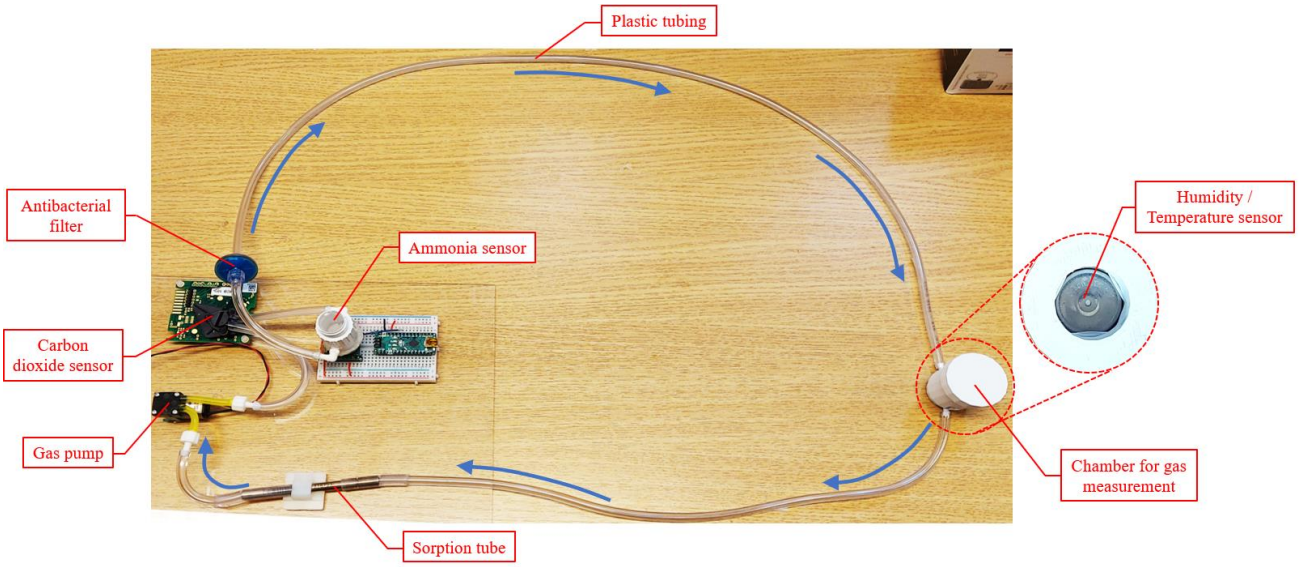

Figure 19. Set up for flowing gases from the chamber to the sensors.

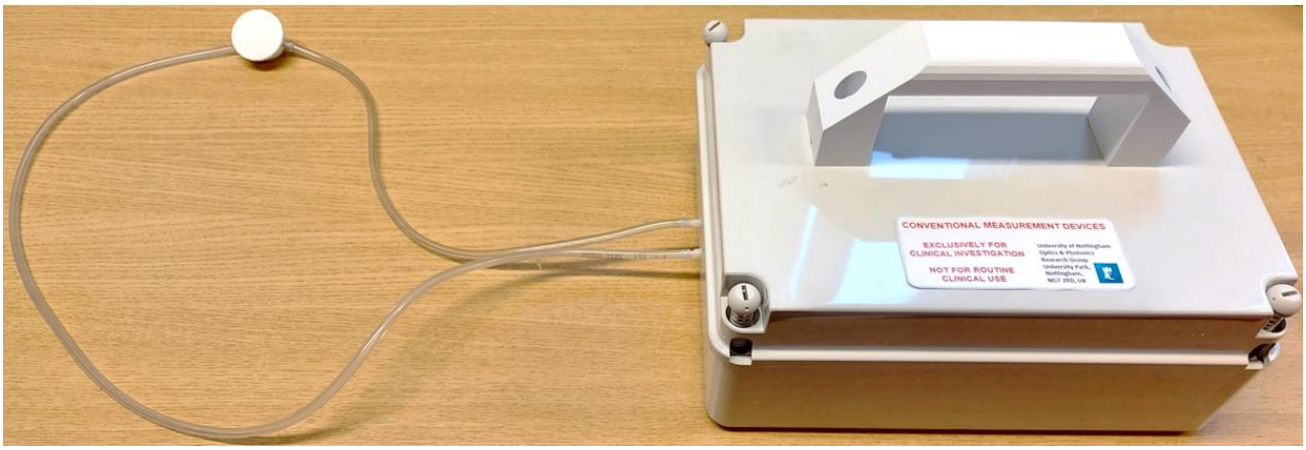

Figure 20. Plastic enclosure for conventional measurement devices setting.

Multiple values per parameter will be recorded over 1 minute recording period and their average will be used for the statistical analyses. The total dataset will include time averaged values of 4 parameters; from 10 patients; on 4 separate occasions (study visits); in static position; at the wound site from the OFSSWM (4 x 10 x 4 x 1 x 1 = 160); and in static position at the wound and control sites from conventional devices (4 x 10 x 4 x 1 x 2 = 320).

Whilst the OFSSWM optical probe is in place the patients wound/foot will be video recorded in order to synchronise the video to the signal which would allow us to identify reasons for signals becoming distorted. Video recordings will only be made of the wound area and any identifying marks e.g. tattoo, will be manually removed from the video capture using software.

Measurements will be made with the patient in supine position with the wound dressed. The patients index foot would be video-recorded in order that the recordings can be matched with any potential changes in OFSSWM readings. Usual clinical care will comprise of wound debridement, photography, assessment of offloading footwear, assessment of wound for signs of infection or deterioration of vascular supply and dressing of wound.

The index ulcer will be the only ulcer where the OFSSWM optical probe will be applied. Following debridement ulcers will be cleaned only with sterile water or saline and dressed with non-adherent, inert dressings according to usual clinical practice in the study centre.

Visits

Following the baseline visit, patients will be seen in a further 4 fortnightly visits, with a tolerance of +/- 7 days for the visit windows. Patients will therefore be assessed in clinic at the usual timeframe for review which is approximately every 2 weeks.

At each visit patients will be assessed for the following:

- Continued eligibility for trial participation including capacity to consent.
- Willingness to continue in trial.

- Silhouette digital image and measurement of index ulcer as per usual care.
- Assessment of infection by IDSA criteria.
- Medication check including any new antibiotic prescriptions.
- Assessment of Pain associated with their DFU (100 mm VAS).
- Application of OFSSWM – measurement in supine position on the wound.
- Conventional measurement devices (sampling sensors for CO_2, NH_3, temperature, humidity and pH probe) – measurement in the supine position only, on the wound and on area of intact foot skin.
- Further measurement will be made off site of the volatile organic compounds of the discarded dressing (SIFT-MS) and the gas collected by the sorption tube (GCMS).
- Video recording of wound/foot during the time the OFSSWM optical probe and conventional measurement devices are in place to allow data to be synchronised with any time the signals become distorted and establish any reasons why.
- Reporting of device related AEs/SAEs.

Study Specific Equipment

Study specific equipment used for this study includes:

- SIFT-MS and plastic bags to contain removed dressing.
- Gas collection chamber and sampling sensors (CO_2, NH_3, temperature, humidity).
- pH probe.
- Sorption tube.
- OFSSWM: optical probe; sterile dressing; opto-electronic unit and its mains adapter.
- Video recorder (Single-lens reflex digital camera, D5600 + AF-P DX 18-55 VR DSLR camera, Nikon).

When not in use, the study specific equipment will be held in a secure locked cabinet at UHDB with access only by Investigator Game, the research Podiatrist and Thomas Spicer (Head of Clinical Engineering). The devices will be kept separately to other supplies and labelled accordingly (with the trial labels as described above).

Table of Assessments and Outcomes per study visit

Visit number	Assessments
Visit 1 (baseline)	• Demographics: Age, sex and type of diabetes. • Concomitant Medication: All over-the counter or prescription medication will be recorded. • Laboratory Tests: eGFR and HbA1c – only if not done as part of usual care within last 12 months. • Removal of dressing and capturing in a plastic bag to measure wound gases via SIFT-MS (dressing in place for at least 12 hours prior to removal). • Ulcer status: ulcer area (cm^2) (from Silhouette digital image and measurement of index ulcer as per usual care). • Assessment of ulcer infection by IDSA criteria. • % surface area slough. • Pain in area of ulcer (10cm VAS). • Assessment of peripheral pulses by palpation. • Assessment of neuropathy using 10g monofilament. • Ankle brachial pressure index (ABPI) measurement. • pH measurements of the wound from the wound exudate by a swab. This will be disposed in clinical waste of in accordance with the Human Tissue Act. • Application of OFSSWM optical probe and sterile dressing on the wound bed. • OFSSWM measurement – Carbon dioxide (ppm); Ammonia (ppm); Relative Humidity (%); and Temperature (°C), from the wound bed. Measurement in supine position. • Removal of OFSSWM optical probe and sterile dressing from the wound bed. • Conventional gas measurement: Carbon dioxide (ppm); Ammonia (ppm); Relative Humidity (%); and Temperature (°C), from the wound bed in a supine position for up to 10 minutes (sampling sensors). • Video recording of wound/foot during the time the OFSSWM and conventional measurement devices are in place to allow data to be synchronised with any time the signals become distorted and establish any reasons why. • Removal of the conventional measurement devices and sterile dressing from the wound bed, application of usual wound care and dressing. • Conventional gas measurement: Carbon dioxide (ppm); Ammonia (ppm); Relative Humidity (%); and Temperature (°C), from the intact foot skin in a supine position for up to 10 minutes (sampling sensors). • Device related AEs.

Visit 2,3,4 (follow-up)	• Continued eligibility for trial participation including continued capacity. • Willingness to continue in trial. • Any changes to medications. • Removal of dressing and capturing in a plastic bag to measure wound gases via SIFT-MS (dressing in place for at least 12 hours prior to removal). • Ulcer status: ulcer area (cm^2) (from Silhouette digital image and measurement of index ulcer as per usual care). • Assessment of ulcer infection by IDSA criteria. • % surface area slough. • Pain in area of ulcer (10cm VAS). • Assessment of peripheral pulses by palpation. • Assessment of neuropathy using 10g monofilament. • Ankle brachial pressure index (ABPI) measurement. • pH measurements of the wound from the wound exudate by a swab. This will be disposed in clinical waste of in accordance with the Human Tissue Act. • Application of OFSSWM optical probe and sterile dressing on the wound bed. • OFSSWM measurement – Carbon dioxide (ppm); Ammonia (ppm); Relative Humidity (%); and Temperature (°C), from the wound bed. Measurement in supine position. • Removal of OFSSWM optical probe and sterile dressing from the wound bed. • Conventional gas measurement: Carbon dioxide (ppm); Ammonia (ppm); Relative Humidity (%); and Temperature (°C), from the wound bed in a supine position for up to 10 minutes (sampling sensors). • Video recording of wound/foot during the time the OFSSWM and conventional measurement devices are in place to allow data to be synchronised with any time the signals become distorted and establish any reasons why. • Removal of conventional measurement devices and sterile dressing from the wound bed, application of usual wound care and dressing. • Device related AEs/SAEs.

Participant Duration: Enrolment will begin in November 2022 and cease 6 months later, with the study recruitment closing in April 2023, and hence the total duration of all patients' participation in the entire study will be 8 months and 31 days (including an 8 week follow up period).

Schedule of Assessment

Screening

- Patient fulfils the inclusion criteria and able to attend clinic for 4 visits at 2-week intervals.
- Participant given written information about study.

Visit 1 Baseline visit

1. Informed Consent of patient by Podiatrist (member of the clinical team).
2. Removal of dressing by Podiatrist and store dressing at -70 °C.
3. Baseline assessments and Silhouette imaging by Podiatrist as per Table above.
4. Swab taken by Podiatrist from wound for pH measurement using pH probe. Measurements taken by a member of the engineering team.
5. Set up of video camera by Podiatrist to record conventional measurement devices and OFSSWM.
6. Set up of OFSSWM opto-electronic unit by member of the engineering team and take of baseline measurement at the atmosphere.
7. Application of OFSSWM optical probe and sterile dressing by Podiatrist on wound bed.
8. Measurement with OFSSWM in supine position by a member of the engineering team.
9. Removal of OFSSWM optical probe and sterile dressing from wound bed by Podiatrist.
10. Set up of sterile dressing and conventional measurement devices set by Podiatrist on wound bed.
11. Capture gases into conventional measurement devices set above the wound on supine position for up to 10 minutes for stabilisation (member of the engineering team).
12. Removal of conventional measurement set up and sterile dressing by Podiatrist.
13. Post conventional devices and sterile dressing removal the patients will have wound dressed in the usual way by the Podiatrist.
14. Set up of sterile dressing and conventional devices set by Podiatrist on intact foot skin.
15. Capture gases into conventional measurement devices set above intact foot skin on supine position for up to 10 minutes for stabilisation (member of the engineering team).
16. Removal of conventional measurement devices set up by Podiatrist.
17. Reporting of device related AEs/SAEs by member of the clinical team.

Visit 2, 3, & 4 - Study visits

1. Continued eligibility for trial participation including capacity to consent and willingness to continue in study by Podiatrist.
2. Removal of dressing by Podiatrist and store dressing at -70 °C.
3. Baseline assessments and Silhouette imaging by Podiatrist as per Table above.
4. Swab taken by Podiatrist from wound for pH measurement using pH probe. Measurements taken by a member of the engineering team.
5. Set up of video camera by Podiatrist to record conventional measurement devices and OFSSWM.
6. Set up of OFSSWM opto-electronic unit by member of the engineering team and take of baseline measurement at the atmosphere.
7. Application of OFSSWM optical probe and sterile dressing by Podiatrist on wound bed.
8. Measurement with OFSSWM in supine position by a member of the engineering team.
9. Removal of OFSSWM optical probe and sterile dressing from wound bed by Podiatrist.
10. Set up of sterile dressing and conventional measurement devices set by Podiatrist on wound bed.
11. Capture gases into conventional measurement devices set above the wound on supine position for up to 10 minutes for stabilisation (member of the engineering team).
12. Removal of conventional measurement set up and sterile dressing by Podiatrist.
13. Post conventional devices and sterile dressing removal the patients will have wound dressed in the usual way by the Podiatrist.
14. Set up of sterile dressing and conventional devices set by Podiatrist on intact foot skin.
15. Capture gases into conventional measurement devices set above intact foot skin on supine position for up to 10 minutes for stabilisation (member of the engineering team).
16. Removal of conventional measurement devices set up by Podiatrist.
17. Reporting of device related AEs/SAEs by member of the clinical team.

Concomitant and Rescue Medications and Treatments

All concomitant treatments must be documented on the CRF and also in the participant's medical records. Include any changes to these treatments.

Compliance

There is no minimum data set for the participant to be included in the analysis in the event of withdrawal from the study before all visits have been attended. Data collected up until the point they leave the study will still be used in the analysis. Patients who withdraw will be replaced within the timescales of the study, but all data will be used in the final analysis.

Accountability for devices

The Investigator, or a member of the engineering team, will ensure that all investigational devices are stored in a secure area, under recommended storage conditions and in accordance with applicable regulatory requirements.

To ensure adequate records, all devices will be accounted for in the case report form (CRF) and device accountability forms. At the end of the clinical trial all unallocated, unused or returned devices will be destroyed or returned to members of the engineering team.

Criteria for terminating study

Stopping the study as a whole may be as a result of a major safety concerns, new information, or issues with study conduct (e.g. poor recruitment, loss of resources). Stopping if unacceptable performance in recruitment or compliance with protocol. Members of the engineering team will be responsible for returning or destroying unused trial materials.

TRANSPORT AND STORAGE OF THE SAMPLES

Samples will be stored in a linked anonymised format and labelled using a combination of study reference, unique study identifier and cross referenced with location code numbers to permit accurate linkage to study data and the consent form.

Wound dressing samples will be placed in resealable plastic bags and stored at -70 degrees centigrade.

The master database will be held by the engineering team in a password encrypted file.

The analysis of samples will take place at Brunel University.

Wound dressing samples will be transferred from the study site (University Hospitals of Derby and Burton NHS Foundation Trust (UHDB) Secondary care diabetic foot multidisciplinary clinic) to the respective collaborators (Prof. Claire Turner, Brunel University) in batch shipments by courier as frequently as required. All shipments will contain a complete inventory of all samples, along with the name of the person responsible for sending the samples. Once analysis has taken place, samples will be destroyed in accordance with the Human Tissue Act, 2004.

STATISTICS

Methods

Statistical analysis will be undertaken by the Trial Statistician according to the Statistical Analysis Plan using Stata software. Interim analyses will not be undertaken.

Descriptive statistics, frequencies (%) or median (IQR), will be presented for baseline and feasibility outcomes.

Quantitative sensor data will be recorded; the OFSSWM and the conventional devices will record 4 parameters (humidity, NH_3, CO_2, and temperature) that are potentially associated with wound healing. The pH probe from the conventional devices will also record pH from a swab taken from the wound exudate. A time-series of data will be recorded per parameter. The time series will be presented graphically per parameter using line graphs.

The average value will be used to compare the parameters between the intervention and conventional devices using Paired T-Test. They will be presented graphically using Bland-Altman plots.

The wound size, reduction from baseline, and pain scores will be presented graphically using line graphs, and descriptive statistics across all visits. The rate of secondary infection will be presented at each visit using frequencies (%).

Sample size and justification

This is a feasibility study and so is not powered for statistical testing. 10 participants will provide a sample size of up to 200 measurements for each OFSSWM parameter (humidity, NH_3, CO_2, temperature) at each visit.

Assessment of safety

The optical probe from the OFSSWM has been identified as ‘low risk’ in a biological risk assessment conducted independently on our behalf by North American Science Associates (NAMSA), please see ‘QMS-OFS-TF-16 Biocompatibility Report’. A sterile dressing (provided as part of the OFSSWM) will be used as a barrier between the optical probe and the wound bed.

The opto-electronic unit from the OFSSWM has been assessed by the Clinical Engineering Department at Nottingham University Hospitals NHS Trust as complying with medical device regulations. This information will be found in the device technical file. Please see the document ‘QMS-OFS-TF-07A Electrical Safety’ and ‘QMS-OFS-TF-12 Test and pre-Clinical Data’ for further details.

All safety variables will be collected as device related AE/SAE.

Procedures for missing, unused and spurious data

Missing values will not be replaced as this is feasibility study. All analyses will be undertaken using complete data, and subjects with missing values will be excluded on a per outcome analysis.

Definition of populations analysed

Safety set: All participants.

Full Analysis set: All participants who were eligible to take part in the study. Including intention to treat analysis for any participants that do not complete all study visits.

ADVERSE EVENTS

Definitions

Adverse Events

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study. The study is analysing all data as it is a feasibility study, data will include safety and a full set of data. Therefore deviations (violations) from protocol will not lead to exclusion of a participant from the per protocol set.

We will notify the MHRA of all deviations to the study as soon as you have been made aware of them. Details about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective actions should be provided.

An AE does include a/an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product/device administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a/an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

Adverse Device Effects

An adverse device effect is defined as any untoward and unintended response to a medical device and includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of a user error.

Serious Adverse Events

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Serious Adverse Device Effects

A **Serious Adverse Device Effect (SADE)** is defined as an adverse device effect that resulted in any of the consequences, characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. Note that this definition captures “near misses” as well as actual incidents.

An **unexpected adverse device effect** is any adverse device effect, the specificity or severity of which is not consistent with the current Investigator’s Brochure.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial device which makes a causal relationship incompatible or for which other treatment, drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial device which makes a causal relationship a reasonable possibility, but which could also be explained by other treatments, devices, drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial device which makes a causal relationship a reasonable possibility, and is unlikely to be due to other treatments, devices, drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial device which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study device is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Device Effect.

Recording and Reporting of Adverse Events

All adverse events (AEs) will be recorded as they are reported whether spontaneously volunteered or in response to questioning about well being at trial visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. A note of any concomitant medication will also be made so that a full assessment of the AE can be made.

Abnormal laboratory test results that are deemed clinically significant by the investigator and that lead to a change or temporary or permanent discontinuation in the use of the device, or require intervention or diagnostic evaluation to assess the risk to the subject will be recorded as adverse events or adverse device effects in the CRF and instigate further investigation and follow up as appropriate.

All AEs, SAEs, ADEs and SADEs will be documented in the subject's medical records and CRF. All events must be followed until resolution, or for at least 30 days after discontinuation in use of the device, whichever comes first.

Participants will be asked to contact the study site immediately in the event of any SAEs or SADEs. The Chief Investigator shall be informed immediately of any serious events and shall determine seriousness and relationship in conjunction with any treating medical practitioners.

All adverse events and adverse device effects will be recorded and reported to the MHRA and REC as part of the annual reports.

SAEs and SADEs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator will be responsible for all adverse event reporting.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial device.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed a SAE or SADE, shall, within 7 days, complete the appropriate adverse incident report form available from the MHRA web page and send to the MHRA.
- If the event is deemed serious, related and/or unanticipated to the trial device, shall inform the REC using the reporting form found on the NRES web page within 15 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the REC as required.

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval/favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent

amendments, the UK Department of Health Policy Framework for Health and Social Care, 2017and the Medical Device Directive.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The Investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The Investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The Investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the Investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Device accountability

Device supplies will be kept in a secure, limited access storage area under the storage conditions specified by manufacturer. All components of the study specific equipment will be stored in a locked secure cabinet at UHDB during the study.

Members of the engineering team will maintain records of the study devices delivery to the site, an inventory at the site, and the return to the storage or alternative disposition of unused study devices. These records will include dates, quantities received, batch/serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and/or the local site staff will maintain records that document adequately which OFSSWM probe was used on each participant. These records will be part of each patient's Case Report Form (CRF). All study devices received by the site shall be accounted for.

Case Report Forms

Each participant will be assigned a study identity code number, allocated at consent, for use on CRFs other trial documents. The documents will also use study number and date of birth only (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The clinical Investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Study Number (the Study Recruitment Log), to permit identification of all participants enrolled in the study, in accordance with regulatory requirements and for follow-up as required. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

CRFs are used to record clinical trial data and are an integral part of the trial and subsequent reports. The CRFs, therefore, must be legible and complete. All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated. The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Data from the OFSSWM and conventional measurement devices will be stored in csv (comma separated values) format which is widely supported by different applications. Each data file will represent a recording session (e.g. visit to a clinic) for a specific patient. A time series will be recorded for each OFSSWM optical probe with each column representing a different optical probe parameter. The per patient data files will be merged into a single spreadsheet prior to statistical analyses.

Source documents

Source documents shall be filed at the Investigator's site and may include but are not limited to, consent forms, current medical records, and laboratory results. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall be made available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g., MHRA).

DATA PROTECTION

UoN's Research Filestore is centrally managed and provided by UoN Information Services (IS), and is subject to IS Business Continuity Planning, IS Information Security Policy and IS Change and Release standards including the UoN Backup, Restore and Backup Retention policy. The service includes failover support across two separate data centres. Full backups to tape are performed once a week, while incremental backups are performed nightly. Tapes are retained for 112 days, after which they are re-used or securely disposed of. This service does not provide any long term archiving or data preservation, except by prior arrangement. Access to the service requires authorised UoN credentials, and is restricted by the institutional firewall.

All trial staff (members of the engineering team and clinical team) and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).

Information about the trial in the participant's medical records/hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by the research subjects.

STUDY CONDUCT

The study conduct will be subject to systems audit of the study Master File for inclusion of essential documents; permissions to conduct the trial; study; Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; device accountability, device records and equipment calibration logs.

STUDY DATA

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The study Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required, these will carry a full audit trial and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University Of Nottingham Research Code Of Conduct, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians (members of the clinical team), the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Once sufficient commercialisation progress has been made and intellectual property is protected, we will make raw data available through the University of Nottingham Research Data Repository. We will target major conferences such as Photonics West, IEEE Sensors, the American Diabetes Association and the European Association for the Study of Diabetes and leading journals such as Nature Biomedical Engineering, Biosensors and Bioelectronics, Lancet Diabetes and Endocrinology, Diabetes Care and Diabetologia. We will ensure the user group convened to support development is

updated via an email newsletter. We will participate in public engagement events organised by UoN such as 'Wonder'. In all cases study participants will not be identifiable.

USER AND PUBLIC INVOLVEMENT

Patient views have not been sought with respect to the development of this protocol, but views of the Derby Diabetic Foot PPI group will be sought in a plain English summary of the study for promotion of results, and their views on the design and feasibility of future clinical studies will be sought once the results of this study are known.

STUDY FINANCES

Funding source

This study is funded by the Medical Research Council, U.K. under Grant MR/R025266/1.

Participant stipends and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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