Trial Protocol

Microwave therapy for treatment of precancerous actinic keratoses

Trial Acronym	MTAK
Sponsor	University of Dundee NHS Tayside
Sponsor R&D Number	2016DS12
Funder	Innovate UK
Chief Investigator	Prof Charlotte Proby
REC Number	18/ES/0008
Clinical Trials Unit	Tayside Clinical Trials Unit
Clinicaltrials.gov Number	NCT03483935
Version Number and Date	Version 5 26/09/2018

PROTOCOL APPROVAL

Microwave therapy for treatment of precancerous actinic keratoses

Signatures
The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Prof Charlotte Proby Chief Investigator	Signature	Date
Prof Peter Donnan Individual Responsible for Statistical Review	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
AK	Actinic Keratosis
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
IF	Incidental Findings
ISF	Investigator Site File
PI	Principal Investigator
PIS	Patient Information Sheet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

SUMMARY/SYNOPSIS

Study Title	**Microwave Therapy for treatment of precancerous Actinic Keratosis** MTAK	
Study Design	Medical Device trial Stage 1: Volunteer study to measure the tissue properties of actinic keratosis (AK) prior to microwave therapy. Stage 2: RCT	
Study Population	Adults diagnosed with AK	
Sample Size	Stage 1: Up to 10 Stage 2: Up to 12 randomised	
Planned Study Period	24 months	
Clinical phase duration	Stage 1: Participants will be in the study for 1 day Stage 2: Participants will be in the trial for up to 28 days	
Follow up phase duration	Stage 1: No follow up Stage 2: Participants will be followed up for 4 months	
Stage 1 Primary	Objectives To determine the permittivity of clinically diagnosed thick and thin AK skin lesions on the hand and visible scalp using a measurement device.	Outcome Measures Dielectric permittivity measure, also known as epsilon relative Er, relative to air (Er=1).
Stage 2 Primary	Objectives Evaluate the efficacy of microwave with the Swift instrument treatment versus no treatment on the resolution of AK lesions using visual assessment	Outcome Measures Skin examination with clinical assessments and photographic mapping to confirm resolution of AK.
Stage 2 Secondary	Objectives To evaluate the long-term resolution of AK following microwave treatment	Outcome Measures Skin examination with clinical assessments and photographic mapping to confirm resolution of AK at 2 and 4 months.
	Objectives To evaluate patient acceptability of the use microwave treatment as a therapy for AK	Outcome Measures Number of Adverse Events and patient acceptability
	Objectives Identify the potential mode of action of microwave energy in the treatment of AK	Outcome Measures Changes in biomarkers of cell proliferation, cell survival and cellular stress responses and the expression and activity of other genes in the biopsy tissue.

1 INTRODUCTION

1.1 BACKGROUND

This study is a collaboration between the University of Dundee, NHS Tayside and Emblation Ltd, funded by Innovate UK. Emblation is a Scottish based SME and is an established global leader in the design, development and manufacture of microwave medical devices.

Actinic keratoses (AK) are believed the most common pre-cancerous lesions in humans and are precursors to invasive cutaneous squamous cell carcinoma (cSCC), a malignancy that has more than doubled in incidence in the UK in the last decade due to ageing populations and increased UV exposure (Goon 2017). The UK incidence of cSCC now exceeds 30,000 annually (estimated >50,000 cases/year, Public Health England, unpublished data) with significant health burden and NHS costs. These skin cancers are often multiple, especially in immunosuppressed high-risk populations. AK are very common “sun damage” skin lesions found on sun-exposed areas of the skin, such as the backs of hands and bald scalp. Up to 70% of our elderly population have AK (Eder 2014) and 65% of cSCC arise from previously identified AK (Criscione 2009). AK are readily identified clinically so AK treatment offers an important opportunity for cancer prevention, but our ability to treat is limited by undesirable local adverse reactions from existing topical treatments which fail to balance effectiveness, side effects and cost. None of the currently available treatments for AK are suitable for widespread use in the community and are only partially effective. Other more effective treatments such as photodynamic therapy are expensive and time consuming and need to be delivered by experts in secondary care. NHS dermatologists are already overburdened and elderly patients with AK do not wish to travel. AK therapy would be greatly improved by a cheap, convenient, well-tolerated and efficacious therapy that can be delivered closer to home by GPs or nurses.

Clinically, AK display a spectrum of severity from mild Grade 1 lesions, which are just visible and just (barely) palpable, through Grade 2 red and scaly lesions (easily felt and seen), to the most severe Grade 3 lesions, which are grossly hyperkeratotic and “thickened” skin lesions. In practice, it is easier to grade them as ‘thin’ (just palpable) or ‘thick’ (with substance to them). It is possible that the dielectric properties of Thick and Thin AK will differ and therefore the measurement study will need to be carried out on both types of AK such that the appropriate microwave dose can be given to these variable skin lesions.

1.2 RATIONALE

Our hypothesis is that localised microwave energy therapy is a suitable treatment for Actinic Keratosis (AK) skin lesions.

The use of microwave technology is well established as ablative doses for treatment of malignancy e.g. hepatocellular carcinoma (see refs Poggi, Wang, Liang and Martin). There are no known studies using microwave for treatment of pre-cancerous skin conditions or skin cancers. Furthermore, there is very little understanding of the biological process evoked by localised microwave exposure in the skin or of the clinically-relevant biological mechanisms triggered.

Emblation already have a CE-marked microwave instrument used successfully for the treatment of plantar viral warts, the SWIFT device. We now wish to undertake a feasibility trial in 12 participants, each with multiple AK on dorsal hand skin or bald scalp or both. The trial will examine the tolerability, acceptability, efficacy and long-term resolution of AK following one or more treatments with microwave energy delivered using the SWIFT device.

Previous studies performed by Emblation using SWIFT on plantar viral warts found it to be effective and safe (Bristow 2017). Some participants experienced minor discomfort during the microwave therapy but any pain stopped when treatment stopped. Some reddening of the skin at the treatment site may occur but this resolved after 24 hours. Some instances of a haematoma have been seen at larger doses, typically resolving within 7 days.

This will be a two-stage study, stage 1 to measure the electrical properties of AKs in patients. The data from stage 1 allows derivation of the power settings to be used with SWIFT for AK in stage 2, to conduct a randomised controlled trial of microwave treatment, delivered using SWIFT, versus no treatment.

The SWIFT device has variable power and duration controls, the protocol suitable for plantar viral warts is unlikely to be compatible with AK. Plantar warts (verrucas) are considerably thicker than AK and are located on much thicker, more robust areas of normal skin. AK are most common in the elderly population and are located on thinner, more delicate skin. We therefore anticipate that AK will require a smaller dose of microwave energy than plantar warts. In order to derive the correct power and duration settings for the Swift instrument and impart the correct amount of electromagnetic energy (referred to as dose) into the AK, the dielectric properties of AK need to be determined to confirm how the specific tissue responds to the electromagnetic energy (microwave). By measuring relative permittivity (commonly abbreviated to Epsilon relative Er) the dielectric properties of the AK can be determined.

The established method of measurement requires the tissue/material under test to come into contact with a specially designed probe attached to an instrument that measures the response to a radiated signal at the same frequency (8GHz) as that used in Emblation's product "Swift". There are a number of instrument and probe manufacturers e.g. Keysight (HP/Agilent), SPEAG, Anritsu. The probe can be used to test solids, liquids and biological tissues by placing the probe in direct contact for a few seconds whilst remaining still during data acquisition by the instrument.

The instrument (Anritsu MS46122A) providing the probe excitation conforms to the following standards: CE Mark, Low voltage (2006/95/EC) and Safety (EN 61010-1:2010). The energy imparted into the lesion for the measurement will not exceed 0.5mW, by way of comparison this is far less than a mobile phone (up to 500mW) and a FitBit (1.6mW) thus there is no inherent danger to the volunteer.

Emblation employees will operate the instruments and direct the subjects to the probe. Other study team staff may work in conjunction with NHS staff at the time of recruitment and/or at the time of measurement.

Microwave energy is converted to heat in the skin layers and forms the basis of the therapy. The target temperature of 43-46C is crucial in eliciting the correct immune response in the tissue. As the current instrument is 'tuned' with an antenna for plantar warts, it may not be as efficient at imparting the energy into the AK lesions and the target temperature may not be achieved with the same power and duration settings. Conversely, if the AK provides a more efficient conversion of microwave to temperature, potentially too high a temperature may be reached at a given power and duration combination. Stage 1 data will be analysed to model the efficiency of the current antenna in computer simulations and values for input power (W) and duration (s) will be derived from the modelling data, subsequently to be used in the stage 2 of the trial. This will provide the correct dose of microwave energy to be used in Stage 2.

Once the settings required for AK have been determined, we will recruit participants into Stage 2 in order to determine efficacy, long term resolution, tolerability and potential mode of action of microwave treatment for AK.

2 STUDY OBJECTIVES & OUTCOMES

This is a two-stage feasibility study to determine if focussed microwave energy is a suitable treatment for AK.

The two study stages are as follows:

Stage 1:

To determine the electrical properties of permittivity in AK on the hand and bald scalp for subsequent optimisation of the SWIFT instrument to provide the correct dose of microwave energy to the AK.

Stage 2:

1. Evaluate the efficacy of microwave energy as a treatment for AK
2. Evaluate the long-term resolution of AK following microwave treatment
3. Assess the feasibility and acceptability of using microwave energy as a treatment for AK
4. Identify the potential mode of action of microwave energy in the treatment of AK

Table 1: Stage Primary Objective and Outcome Measures

Primary Objective:	Outcome Measure:	Time point of outcome measured
To determine the permittivity of clinically determined thick and thin AK on the hand and balding scalp using measurement equipment.	Dielectric permittivity (Er) measurement relative to air	Each AK measured up to 6 times on a single occasion

Table 2: Stage 2 Primary Objectives and Outcome Measures

Primary Objective:	Outcome Measure:	Time point of outcome measured
Evaluate the efficacy of microwave therapy versus no treatment on the resolution of AK lesions using visual assessment	Full or partial resolution of the AK assessed by skin examination	Baseline (day 0) versus day 8, day 15, day 28, day 42, day 60 and day 120

Table 3: Stage 2 Secondary Objectives and Outcome Measures

Secondary Objective:	Outcome Measure:	Time point of outcome measured
To evaluate the long-term resolution of AK following microwave treatment	Full or partial resolution of the AK assessed by skin examination	Day 60 and day 120
To evaluate patient acceptability of the use microwave energy as a therapy for AK	Number of Adverse Events per participant and patient acceptability	0, day 8, day 15, day 28, day 42, day 60 and day 120
Identify the potential mode of action of microwave therapy in the treatment of AK	Changes in biomarkers of cell proliferation, survival and stress responses and the expression and activity of other genes in the biopsy tissue.	Day 15 OR day 42

3 STUDY DESIGN

3.1 STUDY DESCRIPTION

This study will be delivered in two stages. Stage one is a single site, one day, volunteer study aiming to recruit between 6 and 10 volunteers to identify a minimum of 12 Thick and 12 Thin evaluable AKs. Volunteers with diagnosed clinically typical precancerous AK will be recruited from the Department of Dermatology or Plastic Surgery, Ninewells Hospital, NHS Tayside. Once consented to the study, the clinician will categorize the AKs on the participants hand and/or visible scalp or forehead as either Thick or Thin. Between 3 and 10 AK will be measured using a low dose of electromagnetic energy for up to 6 times and the Er data collected. From this data we will determine the permittivity of the Thick and Thin AK, enabling the SWIFT instrument settings to be optimized for the dose of microwave treatment confirmed. This dose will be chosen for the main trial.

Stage 2: MTAK main trial. The main trial is a 4-month, single site, randomized, internally controlled trial comparing microwave energy therapy versus no treatment, with the participants acting as internal controls. Up to 12 evaluable participants with clinically confirmed precancerous AK on the bald scalp or forehead or dorsal region of the hand will be recruited from the Departments of Dermatology or Plastic Surgery, Ninewells Hospital, NHS Tayside.

Participants will give informed consent after they have received the Participant Information Sheet (PIS) and had adequate time to consider whether they wish to participate in the trial. Participants enrolled in the trial will undergo a screening visit (visit 1) to include a check of inclusion and exclusion criteria, physical exam and medical history. The screening and baseline visits may be combined if the participant is not currently taking any prescribed treatments for AK. Participants taking prescribed treatments for AK will be asked to stop taking the treatment for 4 weeks. If clinically feasible, nonsteroidal anti-inflammatory (NSAID) medication will also be stopped for 4 weeks prior to receiving microwave therapy. At the baseline visit (visit 2) participants will have the AKs on their hands and/or visible scalp recorded on an acetate map and photographed. AK will be graded depending on their thickness as this is used to inform the number of microwave treatments the participant may be given. Thin AK will receive one application of microwave treatment while thick AK may receive two. Participants will be randomized 1:1 to receiving treatment on either the left or right hand, or left or right side of visible scalp. One of the AKs on the side receiving microwave treatment, will be pre-selected for biopsy at a later visit.

Participants will receive microwave energy treatment at the baseline visit. The microwave instrument, SWIFT, manufactured by Emblation and CE marked for dermatology applications, will be used to deliver the microwave treatment. The microwave dose will be between 2 Watt and 4 Watt. The microwave treatment will consist of 3, 2 to 3 second bursts delivered to the same lesion with 5-20 seconds between bursts. These doses have previously been shown to be effective and well tolerated with no adverse events in clinical studies by Emblation in the treatment of plantar viral warts. Up to a maximum of 10 AK lesions per participant will be treated with microwave energy treatment. Participants will be asked about any discomfort experienced at the site of microwave treatment immediately after treatment and 30 minutes after treatment.

Participants will be reviewed at visit 3 (day 8) and visit 4 (day 15) and photographs taken of the AKs on the hands and/or head. If the AK has clinically responded/resolved following the first dose of microwave energy, the biopsy of the predetermined AK will be performed at visit 4 (day 15).

All participants will be contacted by telephone on day 21 (visit 5) to assess any adverse events at the site of treatment and biopsy (if relevant).

All participants will be reviewed at visit 6 (day 28) and photographs taken of the AKs on the hands and/or head. Participants may receive a second dose of microwave energy treatment at Visit 6 (day 28) based on clinical assessments. Participants will be asked about any discomfort experienced at the site of microwave treatment immediately after treatment and 30 minutes after treatment.

All participants will be contacted by telephone on day 35 (visit 7) to assess any adverse events at the site of treatment.

Participants will be reviewed at visit 8 (day 42) and photographs taken of AK on hands and/or head. If the participant received a second application of microwave treatment at visit 6, the biopsy of the predetermined AK will be performed at this visit (visit 8).

All participants will be contacted by telephone on day 49 (visit 9) to assess any adverse events at the site of treatment and biopsy (if relevant).

All participants will be reviewed at visit 10 (day 60) and visit 11 (day 120) with clinical and photographic mapping of AK within treatment and contralateral untreated zones on the hands and/or head. Participants will be asked about their experience of the microwave therapy, for example, what they liked and disliked about it.

Participants will be asked at each visit (face to face and over the telephone) to provide details of any adverse events, in particular at the site of microwave treatment or biopsy, such as if they have experienced any stinging, redness, tingling, numbness or soreness.

3.2 INTERVENTION

Stage 1:
Using the instrument described in 1.2, the sensitivity of the measurement requires cable movements to be minimised between the hardware and sensor component thus it is envisaged that the patient will move and orient themselves such that the tissue area contacts the probe rather than vice-versa. Ergonomics will be considered during the measurement set up to ensure no discomfort will be experienced during the process. To have robust, statistically valid data each lesion will be measured up to 6 times. The total time to achieve a patient measurement set is estimated to be 15 minutes, of which the hand or head will need to be stationary for 10s for each acquisition.

Stage 2:
The microwave treatment will be delivered using the microwave instrument, SWIFT, manufactured by Emblation and CE marked for this indication, will be used to deliver the microwave treatment. A measured dose, determined from data acquired from Stage 1 of this study, will be used per AK. The microwave dose will be between 2 Watt and 4 Watt. The microwave treatment will consist of 3, 2 to 3 second bursts delivered to the same lesion with 5-20 seconds between bursts. Up to a maximum of 10 AK lesions per participant will be treated with microwave energy treatment.

3.3 STUDY FLOWCHART

See appendix 1 for Stage 1 study flow chart and Appendix 3 for Stage 2 study flow chart.

3.4 STUDY MATRIX

See Appendix 2 for Stage 1 study matrix and Appendix 3 Stage 2 study matrix.

3.5 STUDY ASSESSMENTS

Study assessments will be performed according to the Appendix 1, Stage 1 Study Matrix and Appendix 4, Stage 2 Study Matrix. Where study assessments identify any incidental findings these will be communicated to the participants GP, with the participant's consent.

Stage 1 primary end point will be Dielectric permittivity (Er) measurement relative to air.

Stage 2 primary end point is complete or partial resolution of the AK determined by skin examination.
Secondary end points will be:

1) Complete or partial resolution of the AK after 4 months to determine persistence of AK resolution
2) Number of adverse events recorded per participant and patient acceptability to determine participant acceptability of use of microwave therapy for the treatment of AK
3) Changes in expression and activity of biomarkers of cell proliferation, cell survival and cellular stress responses and the expression and activity of other relevant genes and their products in the biopsy tissue

3.6 STUDY SAFETY ASSESSMENTS

3.6.1 Physical examination

A physical examination will be performed at screening to exclude participants with co-morbidities or other clinical disorders that would constitute an exclusion from the study.

3.6.2 Hearing Aids

Participants with AK on the scalp will be asked to remove hearing aids before microwave treatment.

3.6.3 Visual examination

The site of microwave treatment will be assessed at each visit for redness or other inflammation.

3.6.4 Potential discomfort and skin biopsy procedure

Some minor discomfort may be experienced during microwave treatment. As microwave energy initiates heating, the pain will be similar to something hot touching their skin. In other studies, participants found that when therapy was applied for up to 5 seconds, any pain started after 2-3 seconds. Pain stopped immediately when treatment stopped as there is no thermal inertia from the delivery at the tip-lesion interface. Generally microwave was well tolerated. In order to minimise pain, treatment will only be delivered for 2-3 seconds. Microwave treatment may lead to a blanching or reddening of skin at the treatment site. This should go away after 24 hours. Participants will be advised to take simple pain relief such as paracetamol should they suffer any discomfort.

Prior to biopsy, participants will be given an injection of local anaesthetic into skin surrounding the AK and are likely to feel some momentary discomfort (stinging) before the site becomes numb. Thereafter the procedure is painless. Once the local anaesthetic has worn off, the biopsy site may feel painful for 24 hours. Participants will be advised to take paracetamol if needed. Usually, biopsy sites will be closed with a single skin suture that will need to be removed after 2 weeks at the next clinical assessment. Biopsy sites may occasionally bleed or become infected. Participants will have a telephone number to ring for advice and an opportunity to return early if there are any concerns.

3.7 TISSUE

One AK from the microwave treatment allocation will be pre-selected at the baseline visit for biopsy at either visit 4 or visit 7 depending on the treatment regimen adopted by the CI. Part of the biopsy will be sent for routine histopathology. The remainder of the biopsy sample will be sent to the Tayside Tissue Biorepository and expression and activity of relevant genes and their products will be analysed by the research team to identify the cellular pathways activated by microwave energy in the skin. This is a mechanistic investigation, not a genetic test. The research biopsy samples will be retained by Tayside Tissue Biorepository for 5 years.

3.8 INCIDENTAL FINDINGS

Any incidental findings (IF: previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP and/or consultant by the CI or Site PI, with the consent of the participant.

3.9 STUDY POPULATION

Participants with clinically confirmed precancerous AK on the bald scalp or forehead or dorsal region of the hand recruited from the dermatology or plastic surgery outpatient clinics.

3.10 NUMBER OF PARTICIPANTS

Stage 1
Up to 10 participants with clinically diagnosed AK will be recruited from the Department of Dermatology and Plastic Surgery outpatients' clinics Ninewells Hospital, NHS Tayside.

Stage 2
Up to 12 participants with clinically diagnosed AK will be recruited from the Department of Dermatology, Ninewells Hospital, NHS Tayside. Participants will be randomized 1:1 to receive treatment on their left or right hand or left or right side of the visible scalp.

3.11 INCLUSION CRITERIA

The same inclusion criteria will be applied to Stage 1 and Stage 2.

- Male or female participants
- Age 18 years and over
- Clinical diagnosis of precancerous Actinic Keratosis made by a dermatologist
- Able to perform study assessments

3.12 EXCLUSION CRITERIA

The same inclusion criteria will be applied to Stage 1 and Stage 2.

- Inability to give informed consent
- ICD, pacemaker or other implantable device
- Metal implants at site of treatment
- Known allergy or intolerance to microwave therapy
- Unstable co-morbidities (cardiovascular disease, active malignancy, vasculopathy, inflammatory arthritis) which, in the opinion of the CI, would make the patient unsuitable to be enrolled in the study.
- Individuals who are immunosuppressed (organ transplant recipients, haematologic malignancies, HIV).
- Individuals will not be enrolled to the study if they are participating in the clinical phase of another interventional trial or have done so within the last 30 days. Individuals who are participating in the follow-up phase of another interventional trial, or who are enrolled in an observational study, will be co-enrolled where the CIs of each study agree that it is appropriate.

4 PARTICIPANT SELECTION AND ENROLMENT

4.1 IDENTIFYING PARTICIPANTS

Identification of participants is the same for both Stage 1 and Stage 2. Participants will be identified by the CI or members of the clinical care team from the Department of Dermatology, or the Department of Plastic Surgery Ninewells Hospital, NHS Tayside. Clinic lists will be reviewed by the CI or delegate and medical records checked to identify suitable patients who will then either be approached and given the PIS when they attend clinic or will be posted an invitation letter and the PIS. If appropriate, Caldicott approval for this activity will be sought. Contact at clinic will be by the CI or delegate. Postage of the invitation letter and PIS will be carried out by the CI or delegate. Participants will be provided with a patient information sheet at least 24 hours in advance. Members of the study team will call patients after the PIS has been sent out to discuss the study and patients that return the reply slip attached to the PIS to arrange the screening visit.

4.2 CONSENTING PARTICIPANTS

For Stage 1 and Stage 2, participants will be consented by the CI or other members of the research team. Participants will be given at least 24 hours to review the PIS.

When first contact is via letter a PIS will be sent which gives a detailed overview of the study. Participants will be asked to contact the research team if they are interested in the study. When first contact is in a hospital clinic they will be given the PIS and will be asked to contact a member of the research team by telephone or email. Research team contact details will be provided on the PIS.

Individuals interested in taking part will be given at least 24 hours to consider their participation in the study before a screening visit is arranged by the CI or delegate, at which participants will be able to ask any questions about the study. If they decide to participate, written informed consent will be obtained and eligibility criteria confirmed.

Should a participant request to speak with a physician from the study team, the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the appropriate person will be asked for their consent. In all cases the CI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where deemed appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

The original informed consent form will be filed in the trial master file (TMF) and a copy will be given to the participant and a copy filed in the participant's medical notes.

The informed consent process will be conducted in compliance with TASC SOP07: Obtaining Informed Consent from Potential Participants in Clinical Research

4.3 SCREENING FOR ELIGIBILITY

No pre- or post-consent screening will be conducted for either stage of the study. Participants recruited to Stage 2, the RCT, will be required to stop using any prescribed treatment for AK for at least 4 weeks before starting the trial.

4.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

The reason(s) for ineligibility will be explained to participants and any questions they have will be answered. They will be thanked for their participation in screening and any relevant information from this will be added to their hospital notes and be communicated to their GP and consultant where the patient consents for this to happen. Patients will be asked if they wish to rescreen if they meet the criteria described above.

4.5 RANDOMISATION

4.5.1 Randomisation

Stage 1 is not randomised. Randomisation in stage 2 will be performed by TCTU using TRuST, a web based, GCP compliant randomization system. There will not be any stratification or minimisation.

4.5.2 Intervention Allocation

The site of treatment, scalp or hand, is a clinical decision made at the time of the baseline visit. Randomisation will be to treatment of the left or right hand, or randomisation to treatment of the left or right side of the visible scalp. There will be no stratification or minimisation.

4.5.3 Withdrawal procedures

If participants withdraw from microwave treatment, the study team will ask them if they are willing to remain in the trial and complete trial assessments. If a participant withdraws from the trial and does not wish to return for trial visits, contact with them will be maintained by the CI or delegate to ensure resolution of adverse events. If withdrawal is due to an AE, it will be recorded on the CRF and AE log.

All participants will be asked about any adverse events at each visit and these will be recorded in the trial AE log.

Participants are free to withdraw from the trial at any time. The reason, if known, will be recorded in the CRF and participants medical notes.

Although a participant is not obliged to give reason(s) for withdrawing prematurely, if the participant appears lost to follow up, the CI will make a reasonable effort to ascertain the reason(s), while fully respecting the individual's rights, and will demonstrate that everything possible was done in an attempt to find any participant lost to follow-up. Those lost to follow-up or withdrawn will be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

5 DATA COLLECTION & MANAGEMENT

5.1 DATA COLLECTION

The CI will maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's case notes.

5.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, TASC SOP53 Data Management Systems in Clinical Research.

The data management system (DMS) will be Excel as approved by Sponsor.
The DMS will be based on the protocol and CRF for the study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the study and to ensure the eligibility and safety of the participant. The study database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.

The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 1998, which brought UK law into line with the EU Data Protection Directive. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the study team.

Database lock will be conducted in compliance with TASC SOP32 Locking Clinical Study Databases.

6 STATISTICS AND DATA ANALYSIS

6.1 SAMPLE SIZE CALCULATION

There have been no previous randomised controlled trials of the effects of microwave energy as a treatment for AK. However, it is expected that microwave energy is converted to heat in the skin layers and forms the basis of the therapy as seen in the successful treatment of plantar viral warts. This is a pilot study to compare the effect of microwave treatment against no treatment of AKs with participants acting as their own internal controls.

It is expected that the number of AKs will be approximately the same number left and right and over the 12 proposed patients it should equal out even if not exactly matched within an individual patient.

Assuming we recruit 10 participants, the participants will have multiple AK lesions to treat so if we assume a minimum of 3 and maximum of 10 AK per patient within the treatment zone, there will be between 30 and 100 treated AK and an equivalent number of untreated control AKs; potentially

between 60 and 200 AK. If we assume that there will be 100 AK (50 treated; 50 mapped and followed but not treated) with on average 10 per patient, this will result in approximately 50 lesions in which to assess both efficacy and how tolerable the treatment is. Given 50 treated vs 50 untreated in a paired analysis with McNemar's test then power is 80% to detect a difference in proportion >25% full or partial resolution of 0.33. Given the repeated measures of AK over say 6 visits then we will have 300 paired measurements. Based even on a smaller mean number of visits of say 3 then the number of pairs is increased by the inflation factor (IF) to 55 assuming ICC = 0.05. Hence with a mean of 3 visits ie. 150 paired measurements power would be 80% to detect a difference of 0.2 between treated and untreated in proportion >25% full or partial resolution.

6.2 PROPOSED ANALYSES

The unit of analysis will be the individual AK lesion. The comparison will be within subject between left and right sides or vice versa. Analysis will follow the guidance of ICH E9 and based on intention-to-treat. The primary outcome will be full or partial resolution of the AK, which at the lesion level is binary and so non-linear models will be utilised. Random effects for subject and visit (up to 6) will be modelled with mixed models. The main parameter will represent treated vs. untreated differences. Adjustment will also be made for baseline, gender, age, skin site of treatment and AK subtype.

Analyses will be implemented in SAS 9.4 and quality control of programs will follow the relevant TASC SOPs.

6.3 MISSING DATA

Mixed models assume data is missing at random (MAR) for visits and all visit data is included and so no multiple imputation will be carried out.

6.4 TRANSFER OF DATA

Delegated research staff will enter the data required by the protocol into the CRFs following training in the definitions and methods used in completing the CRF. On completion of data collection the Investigator must certify that the data entered into the CRFs are complete and accurate.

Data verification and cleaning will be performed as per TASC local procedures.

Post database lock for stage 1 and stage 2, anonymised data will be encrypted and provided to Emblation. All data will be stored on a password protected server with rolling back up in place.

Data preservation and sharing will be in accordance with established procedures at the University of Dundee (see http://www.dundee.ac.uk/library/research/datamanagement/). General laboratory data methods and results will be documented in laboratory notebooks and then analysed and written up for publication for dissemination to the scientific community. All electronic data will be stored on secure personal computers and with rolling off-Site backup – the University of Dundee has central provision for this process. All data and laboratory notebooks will be retained for at least ten years, in accordance with general RCUK guidelines.

7 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

7.1 STUDY MANAGEMENT GROUP

The study will be co-ordinated by a Trial Management Group (TMG), consisting of the Chief Investigator (CI), at least one representative of Emblation, a representative of TCTU representative and a representative of the CRC.

7.2 STUDY STEERING COMMITTEE

The study will not have a separate TSC as the remit will be carried out by the TMG.

7.3 DATA MONITORING COMMITTEE

The study will not have a separate DMC as the remit will be carried out by the TMG.

7.4 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

8 GOOD CLINICAL PRACTICE

8.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHST R&D approval will be obtained prior to commencement of the study.

8.2 CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

8.3 DATA PROTECTION

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

8.4 INSURANCE AND INDEMNITY

The University of Dundee and Tayside Health Board are Co-Sponsoring the study.

Insurance – The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

9 ADVERSE EVENTS

9.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

9.2 RECORDING AND REPORTING AE

All AEs will be recorded on the AE Log in the CRF and will be assessed for severity by the CI or delegate. AEs will be recorded from the time a participant gives consent to join the study until the participant's last study visit.

The CI will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. SAEs will be followed up until 30 days after participant's last visit.

The CI or delegate will ask about the occurrence of AEs and hospitalisations at every visit during the study. **SAEs which are both unexpected and related to study participation** will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

Worsening of the condition under study will not be classed as an AE, but will be defined as an outcome. Pre-specified outcome(s) will not be classed as an AE but as an outcome. Elective admissions and hospitalisations for treatment planned prior to randomisation, where appropriate, will not be considered as an AE. However, SAEs occurring during such hospitalisations will be recorded.

10 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

11 STUDY CONDUCT RESPONSIBILITIES

11.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHST R&D Office. Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

11.2 STUDY RECORD RETENTION

Archiving of study documents will be for 5 years after the end of study.

11.3 END OF STUDY

The end of study is defined as database lock. The Sponsor, CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

12 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

12.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Publications will be reviewed according to the agreed contractual terms of the grant funding but will not restrict the general rights outlined above for Investigators to publish the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

12.3 PEER REVIEW

This project has been peer reviewed by the funder, Innovate UK, an executive non-departmental public body, sponsored by the Department for Business, Energy and Industrial Strategy. The protocol has been peer reviewed by the Sponsor and by Emblation, the industrial partner on the grant award.

13 REFERENCES

Bristow I, Lim WC, Lee A, Holbrook D, Thomson P, Webb C, Polak M, Ardern-Jones MR. Microwave therapy for cutaneous human papillomavirus infection. Eur J Dermatol 2017; 27(5): 511-8

Criscione BD, Weinstock MA, Naylor MF, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009; 115: 2523-30.

Eder J, Prillinger K, Korn A, et al. Prevalence of actinic keratosis among dermatology outpatients in Austria. Br J Dermatol 2014; 171: 1415-21

Goon PK, Greenberg DC, Igali L, Levell NJ. Squamous Cell Carcinoma of the Skin has More Than Doubled Over the Last Decade in the UK. Acta Derm Venereol. 2016; 96(6):820-1.

Liang P, Wang Y, Microwave Ablation of Hepatocellular Carcinoma. Oncology 2007;72(suppl 1):124-131

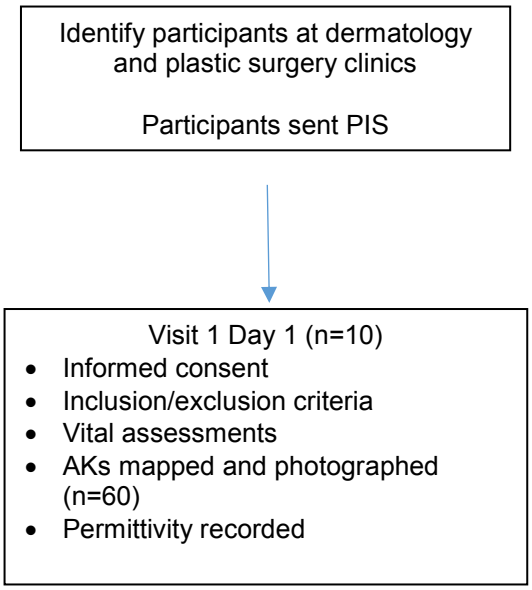
Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988; 8589: 795-7

Martin R.C.G. (2011) Microwave Ablation and Hepatocellular Carcinoma. In: McMasters K. (eds) Hepatocellular Carcinoma:. Springer, New York, NY

Poggi G, Tosoratti N, Montagna B, Picchi C. Microwave ablation of hepatocellular carcinoma. World Journal of Hepatology. 2015;7(25):2578-2589.

Wang T, Lu XJ, Chi JC, Ding M, Zhang Y, Tang XY, Li P, Zhang L, Zhang XY, Zhai B. Microwave ablation of hepatocellular carcinoma as first-line treatment: long term outcomes and prognostic factors in 221 patients. Sci Rep. 2016 Sep 13;6:32728.

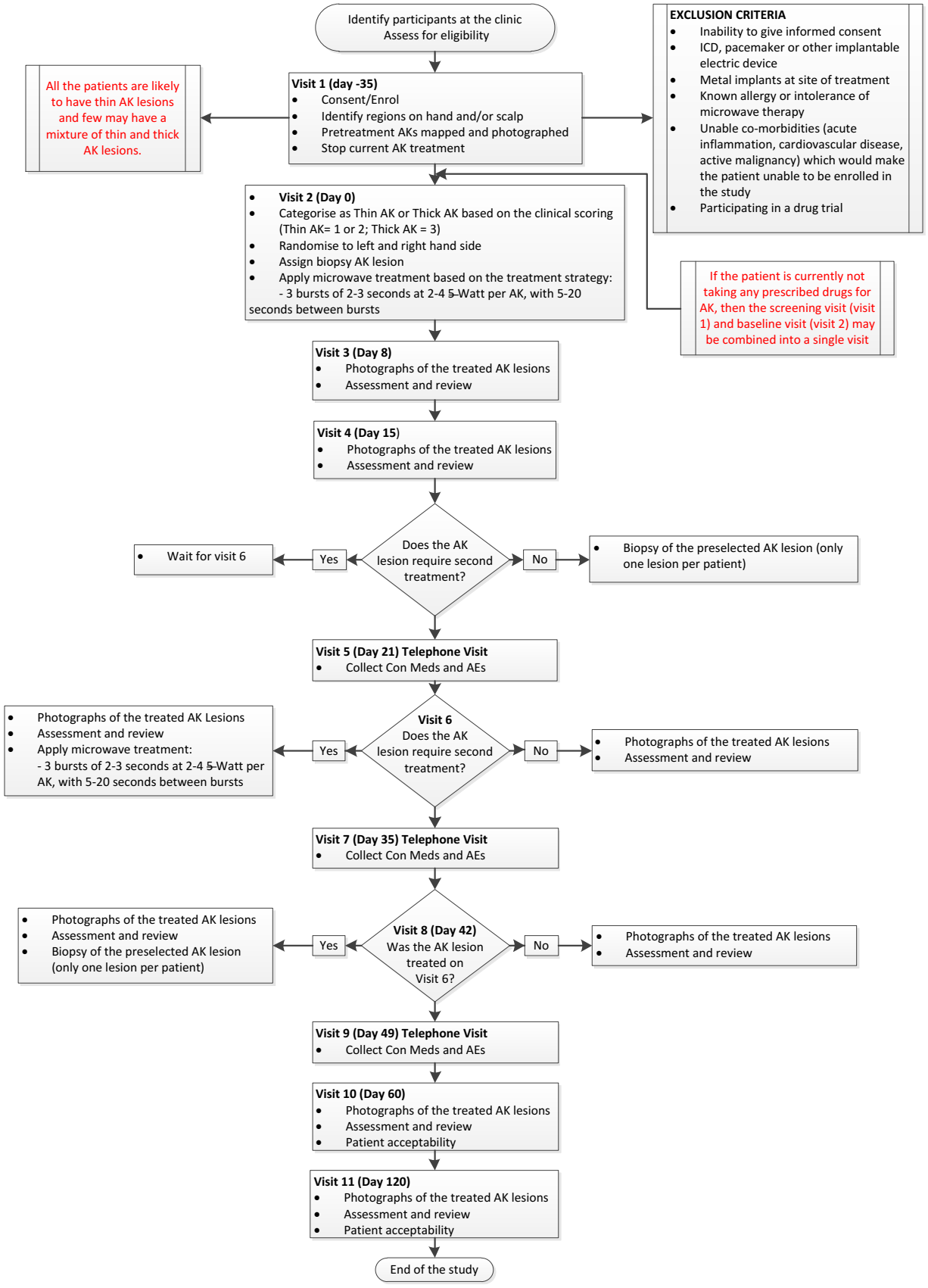
APPENDIX 1: STAGE 1 STUDY FLOWCHART



APPENDIX 2: STAGE 1 STUDY MATRIX

Type of Visit	Baseline
Timeline	Day 0
Informed consent	X
Inclusion/Exclusion	X
Medical History	X
Con meds	X
Physical Exam	X
Permittivity Assessment	X
Record AEs	X

APPENDIX 3: STAGE 2 STUDY FLOW CHART



APPENDIX 4: STAGE 2 STUDY MATRIX

	Visit 1[1]	Visit 2[1]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Type of Visit	Screening	Baseline									
Timeline	-35 days	Day 0 (+/-3 days)	Day 8 (+/-3 days)	Day 15 (+/-3 days)	Day 21 (+/-3 days)	Day 28 (+/-3 days)	Day 35 (+/-3 days)	Day 42 (+/-3 days)	Day 49 (+/-7 days)	Day 60 (+/-7 days)	Day 120 (+/-7 days)
Informed consent	X										
Inclusion/exclusion	X										
Medical History	X										
Con Meds	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X		X		X		X	X
Stop current AK treatment	X										
Map AK	X	X	X	X		X		X		X	X
Photograph AKs	X	X	X	X		X		X		X	X
Categorise type of AK as Thin or Thick		X									
Randomisation		X									
Pre select AK for biopsy		X									
Microwave treatment of up to 10 AKs per participant		X				X[2]					
Visual assessment of treated AKs		X	X	X		X		X		X	X
Biopsy				X[3]				X[3]			
Patient Acceptability		X	X	X	X	X	X	X	X	X	X
Record Adverse Events		X	X	X	X	X	X	X	X	X	X

Notes
1: Screening visits and baseline visit may be combined if participant is not on currently prescribed treatment for AK
2: Second treatment is based on clinical opinion of CI or delegate
3: Biopsy performed once during the study. This will be performed at visit 4 if no second microwave treatment. If second treatment given, biopsy taken at visit 8, not visit 4.