MTAK
Statistical Analysis Plan

TRIAL FULL TITLE	Microwave therapy for treatment of precancerous actinic keratosis		
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2 ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AK	Actinic Keratosis
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
TMG	Trial Management Group
TCTU	Tayside Clinical Trials Unit

3 INTRODUCTION

3.1 PREFACE

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). 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.

Our hypothesis is that localised microwave energy therapy, delivered by a device called SWIFT, is a suitable treatment for Actinic Keratosis (AK) skin lesions. MTAK is a two-stage feasibility study to determine if focussed microwave energy is a suitable treatment for AK. The results of stage 1 have been analysed and this SAP describes the statistical analyses for stage 2 only.

3.2 PURPOSE OF THE STAGE 2 ANALYSES

Evaluate the efficacy of microwave with the SWIFT instrument treatment versus no treatment on the resolution of AK lesions.

3.3 REFERENCE DOCUMENTS

This Statistical Analysis Plan has been prepared in accordance with statistical analyses described in the protocol (version 5, dated 26Sep2018) and data collected according to the case report form (version 1, dated 26Apr2018). The data were transcribed from paper to Excel by the research nurse in a pre-specified format (MTAK_DataCollectionFormat_V3_06Sep2018.xlsx). The table shells referenced to in this SAP are in the document MTAK_TableShells_V1_13Feb2019.docx.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 STUDY OBJECTIVES

Primary objective: Evaluate the efficacy of microwave energy as a treatment for AK

Secondary objectives:

(a) Evaluate the long-term (2 – 4 months) resolution of AK following microwave treatment
(b) Evaluate patient acceptability to use of microwave energy as a treatment for AK
(c) Identify the potential mode of action of microwave energy in the treatment of AK

Note that objective (c) will be addressed by additional data which will be collected separately to that for the primary and secondary (a) and (b) objectives and so will be covered by a separate SAP. This objective will not be discussed further in this analysis plan.

4.2 ENDPOINTS

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	Visits 3 (day 8), 4 (day 15), 6 (day 28), 8 (day 42), 10 (day 60) and 11 (day 120)
To evaluate the long-term resolution of AK following microwave treatment	Full or partial resolution of the AK assessed by skin examination	Visits 10 (day 60) and 11 (day 120)
To evaluate patient acceptability of the use microwave energy as a therapy for AK	Pain levels during and following treatment	Visits 2 (day 0) and 6 (day 28)

4.3 DERIVED VARIABLES

Variables to represent the primary and secondary outcome measures will be derived as follows:

Objective:	**Outcome Measure:**	**Derivation**
Primary	Full or partial resolution of the AK assessed by skin examination	See "Visual Assessment of AKs" tables in CRF. For each lesion (treated and untreated) at each relevant time point: • "Response" = "Complete Resolution" or "Partial Resolution %)" • "No response" = "No change" Assessed at visits 3 (day 8), 4 (day 15), 6 (day 28), 8 (day 42), 10 (day 60) and 11 (day 120)
Secondary	Full or partial resolution of the AK long term assessed by skin examination	As primary endpoint but assessed at day 60 and day 120
Secondary	Patient Acceptability – pain during treatment	For each lesion treated: • 1 = "Mild" • 2 = "Moderate" • 3 = "Severe" Assessed at visit 2 (day 0) and, if second treatment, visit 6 (day 28)
Secondary	Pain Acceptability – pain following treatment	For each patient, immediately after and 30 minutes after treatment: • 0 = "None" • 1 = "Mild" • 2 = "Moderate" • 3 = "Severe" • 4 = "Unbearable" Assessed at visit 2 (day 0) and, if second treatment, visit 6 (day 28)

5 STUDY METHODS

5.1 GENERAL STUDY DESIGN AND PLAN

This study will be delivered in two stages.

Stage 1 was 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. The clinician categorized the AKs on the participants hand and/or visible scalp or forehead as either Thick or Thin. Between 3 and 10 AK were measured using a low dose of electromagnetic energy for up to 6 times and the Er data collected. From this data the permittivity of the Thick and Thin AK were determined, enabling the SWIFT instrument settings to be optimized for the dose of microwave treatment confirmed. This dose was chosen for the main trial.

Stage 2 is the MTAK main trial, 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. The details of each study visit are described in the protocol in section 3.1 and appendix 3.

5.2 Inclusion-Exclusion Criteria and General Study Population

5.2.1 Inclusion Criteria

Participants will be eligible if they meet the following criteria:

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

5.2.2 Exclusion Criteria

The exclusion criteria are as follows:

- 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.

5.3 Randomisation

Participants will be randomised 1:1 to receive treatment on their left or right hand, or their left or right side of the visible scalp. Randomisation will be performed by TCTU using TRuST, a web based, GCP compliant randomization system. There will not be any stratification or minimisation.

5.4 Study Variables

The table below, from Appendix 4 of the protocol, is a summary of study visits (either by hospital appointment or telephone calls) and data collected at each.

	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	Screen-ing	Base-line									
Timeline	-35 days	Day 0 [a]	Day 8 [a]	Day 15 [a]	Day 21 [a]	Day 28 [a]	Day 35[a]	Day 42[a]	Day 49[b]	Day 60[b]	Day 120[b]
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]			
PROMS		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.
a: +/- 3 days
b: +/- 7 days

For visits 2 to 8, when the main clinical assessments are made, visits should occur +/- 3 days within the scheduled date. For visits 9 to 11, when patients are in follow-up, visits should occur +/- 7 days within the scheduled date. Multiple visits or visits outside these windows will be discussed at data lock and decisions made regarding inclusion of data in the analyses.

An Excel workbook was designed to capture all the data collected on paper versions of the CRF. The "Variables" sheet of "MTAK_DataCollectionFormat_V3_06Sep2018.xlsx" lists all study variables, and includes a description and format for each within the relevant sheets on the workbook.

6 Sample Size

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 i.e. 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.

7 General Considerations

7.1 Timing of Analysis

The analysis will be performed following the final visit by the final patient allowing time for reporting of any serious adverse events (SAEs).

7.2 Analysis Population

The population used in all efficacy analyses will be the Full Analysis Set (FAS) based on intention-to-treat. Therefore all randomised participants will be included and lesions will be assigned the treatment they are randomised to but not necessarily the one received.

The safety population is defined as all participants who received any microwave treatment and excludes those who withdrew from the study prior to receiving any microwave treatment. This population will be used to summarise adverse events and exposure data.

Discussions at TMG meetings prior to database lock suggest that all patients have been treated as randomised and no participants have withdrawn from the study so it is expected that the FAS and safety population will be the same.

7.3 Covariates and Subgroups

Key covariates in the analysis will be gender, age, skin site of treatment and AK subtype.

Forest plots showing the treatment effect in subgroups defined by each covariate will be performed.

7.4 Missing Data

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

7.5 Interim Analyses and Data Monitoring

No interim analyses will be conducted and the usual remit of a Data Monitoring Committee will be carried out by the TMG.

8 Summary of Study Data

8.1 Summary Statistics

Continuous variables will be summarised by the number of observations, number of missing values, mean, standard deviation (SD), median, and range.

Categorical variables will be summarised by the number of observations, number of missing values and number and percentage in each category.

8.2 Patient Disposition

Patient disposition, to indicate any patient withdrawal from the study, will be summarised in a CONSORT diagram (Figure 1).

8.3 Protocol Deviations

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 Deviations Log. The statistician will be informed of any potential impact on the data.

8.4 Demography and Medical History

The following variables will be recorded at baseline (Visit 1 on CRF):

- Age (years)
- Gender (Female/Male)
- History of skin cancer and other cancer types
- Previous treatment for AK

A table of baseline characteristics will summarise age, gender, history of skin cancer or other cancer (Table 1.1). All cancer types recalled by the participant are listed (Listing 4.1).

Previous treatments for AKs will be summarised in a table (Table 1.2) and their effectiveness (which is a free text field) as a listing (Listing 4.2).

8.5 Prior and Concurrent Medications

Prior and concurrent medications will be recorded at each study visit ("Concomitant medications" page of CRF) and summarised as a listing (Listing 4.3).

8.6 Data Collected on AKs

The following will be recorded at baseline:

- Site of microwave treatment (Scalp/hand)
- Randomisation side (Left/Right)

- Visual assessment of thick/thin for each AK
- The lesion identified for biopsy

The visual assessment of thickness of the AKs will be summarised in a table (Table 1.3). Summaries of site and randomisation side are discussed in the Safety Analyses section.

The AKs will be assessed visually for clinical signs of resolution at visits 3 (day 8), 4 (day 15), 6 (day 28), 8 (day 42), 10 (day 60) and 11 (day 120).

9 EFFICACY ANALYSES

The unit of analysis will be the individual AK lesion. The comparison will be within participant between the treated side (left or right) and the opposite, untreated side. Analysis will follow the guidance of ICH E9 and based on intention-to-treat.

9.1 PRIMARY EFFICACY ANALYSIS

The primary outcome, resolution of the AK, will be determined by partial or full resolution of the AK over all time periods. The resolution for each lesion at each visit will be coded as a binary variable, "response" or "no response" (see section 4.3). Resolution is assessed at 6 visits: 3 (day 8), 4 (day 15), 6 (day 28), 8 (day 42), 10 (day 60) and 11 (day 120).

A table of the number of lesions resolved by treatment group and visit will provide a descriptive summary for the primary endpoint (Table 2.1)

A graph will show the proportion of resolved AKs by visit and treatment group (Figure 2).

To test the treatment effect, non-linear models will be utilised. Random effects for patient and visit (≤6 per patient) will be modelled with mixed models. The main parameter will represent treatment effect as treated vs. untreated differences and will be reported as an odds ratio, 95% confidence interval and p-value corresponding to a hypothesis test of null treatment effect. Visit will be analysed as study day as the visits are not equally spaced in time. Variables representing gender, age, skin site of treatment (hand/scalp) and AK subtype (thick/thin) will be included as covariates (Table 2.2). A forest plot will illustrate any possible differences in response rates for baseline variables (Figure 3).

9.2 SECONDARY EFFICACY ANALYSES

9.2.1 Long term resolution of AK lesion

Long term resolution of AK lesions will be assessed using a similar definition to the primary objective (i.e. resolution is defined as "partial" or "complete" response) but only data from visits 10 and 11 (day 60 and 120) are analysed.

To test the treatment effect, non-linear models will be utilised. Random effects for patient and visit (≤2 per patient) will be modelled with mixed models. The main parameter will represent treatment effect as treated vs. untreated differences and will be reported as an odds ratio, 95% confidence interval and p-value corresponding to a hypothesis test of null treatment effect. Visit will be analysed as study day. Variables representing gender, age, skin site of treatment (hand/scalp) and AK subtype (thick/thin) will be included as covariates (Table 2.3).

9.2.2 Patient acceptability

Patient acceptability will be summarised as pain experienced during and following treatment. Since there is no comparator group and this is a feasibility study, no formal statistical analyses will be performed on pain levels.

9.2.2.1 Pain during treatment

For each lesion, the pain is described as “Mild”, “Moderate” or “Severe”. Given the relatively small number of patients in this study and the expectation of patient-dependent thresholds, a summary table will show counts of lesions in each pain category for each patient at visit 2 and, where appropriate, visit 6 (Table 2.5).

9.2.2.2 Pain following treatment

Participants will be asked about the levels of worst pain and after 30 minutes, with options “None”, “Mild”, “Moderate”, “Severe” or “Unbearable”. They will also be asked about the duration of pain. These data will be summarised in a table, with separate columns for visit 2 and visit 6 (Table 2.6).

9.3 Post hoc Analyses

There is interest in lesion assessment at later visits (i.e. visits 8, 10 and 11 at Days 42, 60 and 120) and any changes to lesion resolution between these visits. McNemar tests will be used to estimate changes between the treatment arms at these time points, specifically response and non-response will be compared at (1) visit 8 vs visit 10, (2) visit 8 vs visit 11, and (3) visit 10 vs visit 11 (Table 2.4). These analyses will not be adjusted for within-participant variation but will provide some descriptive analyses on possible changes in lesion resolution at later visits.

10 Safety Analyses

10.1 Microwave Treatment

Data at the participant level are collected on:

- Site of microwave treatment (Scalp/hand)
- Randomisation side (Left/Right)

Data at the lesion level are collected on:

- visual assessment of thick/thin
- dose
- duration (seconds)
- number of repetitions
- pain (mild/moderate/severe)

10.1.1 Site and treatment

A table will be produced to summarise the number of patients who receive treatment to their hand or scalp, and to their left or right side (Table 3.1).

10.1.2 Exposure

For all patients exposed to microwave treatment (i.e. the safety population), a summary table for lesions will be produced describing dose, duration and number of repetitions, with separate columns by visit to indicate those patients who receive a second dose (Table 3.2).

10.2 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation.

The CI or delegate will ask about the occurrence of AEs and hospitalisations at every visit (including telephone calls) during the study and, if present, graded as mild or severe.

There are AEs of special interest: itching, soreness, stinging, redness, flaking, open sore/ulcer, puss, tingling, numbness. The presence of scarring and de-pigmentation is also assessed at visits 10 and 11.

AE summaries will be based on patients included in the safety population only. A table of AE incidence by visit will summarise the AEs of special interest (Table 3.3), while all the data recorded in the AE log will be provided in a listing ordered by patient ID number and date of onset (Listing 4.5).

10.3 Patient Experience

Patients were asked about their treatment experience at visits 10 and 11. These data will be summarised in a table (Table 3.4), with likes and dislikes also listed (Listing 4.6).

11 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

12 Technical Details

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

13 Listing of Tables, Figures and Listings

See the "MTAK Study Table Shells" document which accompanies this SAP.

Table 1.1 Baseline Characteristics and Medical History
Table 1.2 Recall of previous treatment for AK
Table 1.3 Visual assessment of thickness of AKs
Table 2.1 Summary for Primary Endpoint by Visit