Reflectance Confocal Microscopy (RCM) to diagnose basal cell carcinoma: HS-MAV-003

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Protocol Synopsis

Protocol ID	Version 0.5, 14th February 2017
Protocol Title	HS-MAV-003
Development phase	II
Primary endpoint	Specificity & Sensitivity of RCM in diagnosing Basal Cell Carcinoma in non-pigmented lesions compared to standard histology
Secondary endpoint	Inter- & intra-observer agreement in assessing RCM images
Study design	This is a non-randomised, non-controlled, prospective observational study to look at the efficacy of *in vivo* RCM as a diagnostic tool in the diagnosis of BCC.
Key Inclusion Criteria	Patients 18 years or older with a suspected diagnosis of BCC
Key Exclusion Criteria	Recurrent or otherwise high-risk BCC Patient with basal cell naevus syndrome Patient treated with hedgehog inhibitor medication (vismodegib) Patient not suitable for diagnostic biopsy Location of lesion unsuitable, inaccessible or impractical for scanning with RCM as determined by investigator
Patient Accrual	328 patients over 18 months
Protocol follow-up procedure	None
Chief Investigator	Dr Howard Stevens
Co-Investigators	Dr Martina Ulrich, Dermatologie am Regierungsviertel Berlin.
Other key staff	Dr Ioulios Palamaras Consultant Dermatologist
Host Institution	Skin Care Network Barnet
Funding	None

Study Title:

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Background

Basal cell carcinoma (BCC) is the commonest skin cancer in the UK and its incidence is rising year on year. Extrapolation of data from the East Norfolk and Waveney area of the UK suggests approximately 200 000 patients had 247 000 BCCs treated surgically that in 2010 (this estimate does not include those treated by other means such as cryotherapy, topical chemotherapy, photodynamic therapy or radiotherapy, without histology) [1].

There are many treatments for BCC depending on the subtype. Thin or superficial BCCs (sBCC) can be treated with topical therapies such as 5-fluorouracil, photodynamic therapy or liquid nitrogen (cryotherapy). Thicker, deeper tumours require surgical excision or radiotherapy. Higher risk lesions, or those of the head and neck where there are significant morbidity risks, can be treated using mohs Micrographic Surgery where removal is histologically controlled.

Reflectance confocal microscopy (RCM) is a high resolution, non-invasive method for visualising skin in cellular detail in-vivo. In studies conducted overseas, confocal microscopy has been shown to be highly effective in the diagnosis of Basal Cell Carcinoma [2-5]. Reported sensitivity and specificity for RCM in diagnosing BCC range from 83-100% and 79-97% [6-12]

A 2004 study showed that the presence of two or more criteria is 100% sensitive for the diagnosis of BCC, and with 4 or more RCM criteria present the specificity was 95.7% and sensitivity was 82.9% [6].

A recent study examined the performance of both the wide field Vivascope 1500 and the narrow field Vivascope 3000. While the traditional wide probe RCM (WTP-RCM) provides more coverage of the lesional tissue, the smaller-diameter handheld RCM (HH-RCM) allows better access to limited anatomic locations [12]. Both instruments are available for this study, and either / both will be used depending on anatomic considerations.

Comparison between TWP-RCM vs. HH-RCM was as follows: sensitivity (100% vs. 93%), specificity (78% for both probes), positive predictive value (96% vs. 95%), and negative predictive value (100% vs. 70%) respectively [12]. Studies have also developed diagnostic criteria for BCC subtypes [11].

Should this diagnostic performance be shown to be replicable in an NHS setting, this would represent a significant opportunity to reduce waiting lists and save money, as patients with lower risk lesions could be diagnosed and treated during their first presentation to the skin cancer clinic. This would improve compliance

Recently, NICE guidance (Nov 2015) was issued regarding the use of RCM in the management of skin cancer [13]. They concluded the following:

> “The VivaScope 1500 and 3000 imaging systems show promise but there is currently insufficient evidence to recommend their routine adoption in the NHS…”
>
> “Further research…on using the VivaScope 1500 and 3000 imaging systems is recommended in the following areas:

> …the impact on clinical workflows for melanoma and basal cell carcinoma assessment in secondary care settings.
>
> …the number of confirmatory diagnostic biopsies needed for people with a clinical diagnosis of melanoma before definitive treatment is started."

If RCM is able to accurately diagnose basal cell carcinoma in the majority of lower risk patients then RCM would negate the requirement for diagnostic biopsy before listing patients for definitive treatment.

Aims

We propose to undertake a study to determine the diagnostic utility of using RCM for the diagnosis of Basal Cell Carcinoma (BCC) in a tertiary referral centre as outlined by the recent NICE report (Nov 2015). This will allow an assessment of the potential to avoid diagnostic biopsy within the treatment pathway.

Study Design and Methods

Study Design

This is an observational, non-randomised, non-controlled, prospective cohort study to look at the efficacy of *in vivo* RCM as a diagnostic tool in the diagnosis of BCC.

Study Hypothesis

The hypothesis of this study is that the use of RCM is would enable a reduction in the number of diagnostic biopsies taken before definitive treatment of BCC by at least 50%.

The secondary hypothesis is that the intra- & inter-observer agreement for interpreting the RCM images will have kappa scores 0.6 or greater (indicating good agreement).

Setting

Patients will be recruited from the outpatient clinic of Skin Care Network London.

Participants

The aim is to recruit 328 patients, who fit the following criteria:

1. Age 18 years or older.
2. Patient suspected of having a primary basal cell carcinoma that is a candidate for surgical treatment.
3. Patient willing and able to give informed consent.

Exclusion criteria

1. Recurrent or other higher-risk BCC
2. Patient with basal cell naevus syndrome
3. Patient treated with hedgehog inhibitor medication (vismodegib)
4. Patient not suitable for diagnostic biopsy
5. Location of lesion unsuitable, inaccessible or impractical for scanning with RCM as determined by investigator

6. Patient with co-morbidities such as other skin disease

Informed Consent

The Investigator, or an authorised member of their team, will obtain written informed consent for patients. It is anticipated that patients will be approached regarding participation after diagnosis when they have been identified as having an equivocal lesion requiring biopsy under standard of care.

When obtaining informed consent, investigators must ensure that they adequately explain the aim, anticipated benefits and potential hazards of taking part in the trial to the patient. Investigators should also stress that patients are free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (when possible, 48 hours) to read the appropriate patient information sheet and to discuss their participation with others if requested. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

Patients, who agree to take part, should be asked to sign and date the latest version of the consent form. The Investigator, or an authorised member of their team, must then sign and date the form. A copy of the form should be given to the patient, a copy should be filed in the clinic notes, and the original placed in the site file.

Study Intervention

Patients will be assessed in clinic by a consultant dermatologist. Patients with a non-pigmented lesion suspected to be BCC will be invited to participate. Clinical and dermoscopic images will be taken by the team as part of their routine standard of care. Patients will be invited to participate in the trial and provided with a patient information leaflet. They will be given sufficient time to review the information sheet and ask questions.

Patients will be consented to having confocal microscopy performed of the target lesion before undergoing biopsy for histology. Acceptable biopsy methods will include punch, shave or excision biopsy with the intention of providing a diagnosis. These patients would be having photographs, including dermoscopic images, and a biopsy as part of their standard of care, therefore the only additional intervention is examination with the confocal microscope.

Confocal microscopy will be performed by a trained clinician, either a doctor or nurse specialist. Once the operator is satisfied that the images have been taken to a standard that will allow independent assessors to provide a diagnosis, they will be stored on a secure server and indexed anonymously with reference to the subject's assigned unique trial number. Imaging time is expected to last approximately 15-20 mins per patient. Similarly, the independent trial co-coordinator will archive the clinical images anonymously for future reference. In this way, data will be anonymised to allow blinding of the diagnosis with reference to the images during the analysis phase. The trial co-ordinator will be responsible for maintaining the database containing the patient and lesion information in addition to the images. The co-ordinator will be the only unblinded member of the investigatory team.

The images taken of the tumour by the confocal microscope will be anonymised. These images will then be examined by a different dermatologist who has undergone training in examining confocal images. The images will also be sent to a dermatologist in Berlin who is an expert in interpreting confocal microscopic images – both of these dermatologists will be blinded as to the patient's history and the results of the diagnostic biopsy. The clinicians interpreting the confocal microscope images will be asked to complete the following questions:

1. RCM description: features of BCC.
2. RCM diagnosis: BCC (Y/N); degree of certainty (0=low; 1=possible; 2=almost certain)

3. RCM quality of imaging: 0=low/don't feel confident; 1=acceptable/could be improved; 2=high quality (free text for images scoring 0)

The biopsies will undergo routine processing in our histopathology laboratory as normal and will be analysed by a pathologist who will be unaware of the findings on confocal microscopy.

Statistics

Summary of statistical methods:

The 95% confidence interval for the specificity and sensitivity will be calculated for both observers. For the confocal microscope to be concluded as having a specificity equal to that of the biopsy the lower limit of the 95% confidence interval must not be less than 94%. Similarly for sensitivity the lower limit of the 95% confidence must not be less than 92%. To assess the inter-observer agreement the Kappa statistic will be reported alongside the proportion of agreements and disagreements.

Sample size calculation

For a specificity of 97% with a maximum marginal error of 3% for constructing the 95% confidence interval a sample size of 125 is required. For a sensitivity of 95% with a maximum marginal error of 3% for constructing the 95% confidence interval a sample size of 203 is required. A total sample size of 328 will be required to test both a specificity of 97% and sensitivity of 95% with a marginal error of 3% for both.

Data management and analysis

The Clinical Record Forms (CRFs) must be completed, signed and dated by the Investigator or an authorised member of staff prospectively. The completed originals will be collected by the trials co-ordinator and held in the site file as source documents. It is the responsibility of the Investigator to ensure that CRFs have been completed correctly and that the data are accurate. Entries should be made in ballpoint pen and should be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. All missing and ambiguous data will be queried. The CRF may be amended as appropriate; this will not constitute a protocol amendment. The revised CRF should be used by all participating sites with immediate effect.

The data will be transferred anonymously to a password –secured electronic database. All patients will be pseudo-anonymised. Data will be stored in databases in the Dermatology Department, Skin Care Network, and any copies to be taken off site (for example for statistical analysis or for analysis by the equipment provider) will be anonymised and will be protected by encryption and password. Access will be restricted to medical and research personnel, and appropriate support personnel. Specific trial information will be restricted to Investigators and collaborators. The trial co-ordinator will be responsible for the daily administration of the database.

An initial interim analysis of the data will be planned after 25 patients to ensure the RCM images are of sufficient quality to continue and complete the study. Data validation will be co-ordinated under the supervision of the trial statistician once the recruitment target has been reached. The final analysis and publication of results will be undertaken after all patients have been recruited. The accrual period is estimated to be 12 months but will be continued until sufficient numbers are obtained for the study to reach significance. Once the dataset is complete, assessment of the RCM images by the blinded investigators will take place to allow statistical analysis of the primary and secondary endpoints, namely specificity, sensitivity and kappa statistics. Analysis of the final dataset is expected to take place within 6 months of completion of accrual. Publication is expected within 12 months of completing the trial.

Ethical Issues

The study proposal is subject to approval by the appropriate Ethics Committee, and will adhere to Good Clinical Practice Guidelines. The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical research Involving Human Subjects Act (WMO).

Amendments

Amendments are changes made to the research after a favourable opinion by the accredited Ethics Committees has been given. All amendments will be notified to the Ethics Committees that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the Ethics Committee(s) application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the Ethics Committees and to the competent authority.

Non-substantial amendments will not be notified to the accredited Ethics Committees and the competent authority, but will be recorded and filed by the sponsor.

Annual Progress Report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited Ethics Committee once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

End of study report

The investigator will notify the accredited Ethics Committees and the competent authority of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last follow-up after 1 year.

In case the study is ended prematurely, the investigator will notify the accredited Ethics Committees, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committees and the Competent Authority.

Public disclosure and publication policy

The study documentation must be retained at all times in a secure and protected environment. This will ensure the integrity of the study data is maintained and protects patient confidentiality.

The CCMO (Central Committee on research involving Human subjects) statement according publication policy is obligatory for participants of the HS-MAV-003 Study and the study sponsor. The results of scientific research involving human subjects must be disclosed unreservedly. For the

avoidance of doubt, negative study results will be published. Further information on publication is outlined in the clinical trial agreement.

Registration of the HS-MAV-003 study will be completed following successful ethical approval.

Safety Considerations

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited Ethical Committees if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited Ethics Committees, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

Adverse and Serious Adverse Events (SAE)

The investigator must inform the Sponsor, within **one working day** by telephone or fax, of any serious adverse event. The investigator must also complete and forward a serious adverse event form within **four calendar days** to the Skin Care Network Research & Development Department. The investigator will be asked to assess the serious adverse events causal relationship to the study device. All SAEs will be reported for up to 30 days post-biopsy and RCM scanning

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.
A serious adverse event is any untoward medical occurrence that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

Data Safety Monitoring Board

Not applicable to this study

Sponsorship & Indemnity

This trial is sponsored by the Medical Advisory Committee (MAC) of the Skin Care Network. The trial is being coordinated by Skin Care Network. These offices do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. There are no specific arrangements for compensation made in respect of any serious adverse events

occurring though participation in the study, whether from listed side effects, or others yet unforeseen. Skin Care Network has a duty of care to patients receiving treatment, whether or not the patient is taking part in a clinical trial. Compensation is only available via Clinic and consultant medical indemnity policies and only in the event of proven clinical negligence.

Publication Policy

All presentations and publications, including abstracts, relating to or arising from, the trial must be authorised by the Trial Management Group / Steering Committee and the Chief Investigator.

Serious Adverse Events (SAE)

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