CLINICAL STUDY PROTOCOL

v3.1 date 2019 Apr 05

TESTING NOMELA® ON SUSPICIOUS PIGMENTED NAEVI:
A HOSPITAL-BASED STUDY

Integrated Research Application System:	254451
Cambridge University Hospitals R&D:	A094925
Moletest (Scotland) Ltd. Study Code:	nomela® C8
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Moletest (Scotland) Ltd.

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1.0 INTRODUCTION

1.1 Brief epidemiology of cutaneous melanoma

Of all cancers in the UK those of the skin are the commonest and comprise predominantly malignant melanoma, squamous cell carcinoma and basal cell carcinoma.

In the UK (2014), melanoma is the 5th most common cancer, accounting for 4% of all new cases of cancer (males: the 6th most common cancer, 4% of all male cases) (females: the 5th, 4% of all new cases).

Highlight figures: UK (2014): new cases of melanoma 15419, deaths 2459, (2% of all cancer deaths) with 10y survival (England&Wales) at 90%.

The projections for incidence rates of cutaneous melanoma are a rise by 7% in the UK between 2014 and 2035 to 32 cases per 100,000 people by 2035 with a larger increase for males than for females.

Skin cancer statistics | Cancer Research UK
www.cancerresearchuk.org/health-professional/cancer-statistics/statistics.../skin-cancer searched 2017nov

Worldwide, the incidence of invasive malignant melanoma is increasing faster than any other cancer
(see references).

Excessive exposure to ultraviolet radiation in sunlight and especially when associated with sunburn is considered the prime predisposing factor which can be ameliorated by behavioural adaptation including the use of headwear, appropriate clothing and sunblock creams . Skin type or colour is also a crucial factor. Underlying genetic predisposition is also relevant where a first-degree relative has a history of malignant melanoma
(Skin Cancer prevention NICE Guidelines PH32 January 2011; Cancer Research UK Sunsmart; US National Cancer Institute-General Information about Melanoma).

1.2 Impact of clinical demands on the NHS

The large majority of pigmented moles are benign but concerns about the possibility of malignancy place a substantial load on health services. The proportion of patients who present in primary care concerned about moles who are referred on to dermatologists at secondary care centres with suspicion of malignancy is not well documented. Nonetheless a substantial proportion of those referred are considered by the

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dermatologist to be benign by inspection without the need for mole removal and histology. When considered needed by the specialist patients are referred for excision biopsy and histology of the suspect lesion.

At Addenbrooke's Hospital the patients with pigmented cutaneous lesions which the specialist dermatologist/plastic surgeon on routine grounds considers require histopathology for diagnosis are normally sent for medical photography of the lesion(s) prior to the excision biopsy.

In Cambridge up to 1 in 10 of pigmented moles referred by specialist dermatologists for excision and histology are found to have melanoma (personal communication Dr N Burrows).

There is thus room for using supporting methods or techniques to aid clinical decision making.

Management of potential melanoma lesions in England is guided by the Revised U.K. Guidelines for the management of melanoma 2010 British Association of Dermatologists, British Journal of Dermatology (2010) **163**, 238-256; NICE Guidelines: Skin Cancer (22/08/2017) https://pathways.nice.org.uk/pathways/melanoma; and NICE Guidance: Melanoma assessment and management [NG14] (2015) http://bit.ly/2sdpnjW or https://www.nice.org.uk/guidance/guidance/ng14

1.3 The nomela® test: using innovative technology to assist diagnosis

The innovative technology of the nomela® test aims to provide the clinician with a tool which, in suspicious pigmented skin lesions (moles), helps to exclude melanoma without biopsy, thereby providing a means of reducing referral rates for biopsy and histopathology.

1.3.1 Moletest Ltd. has developed a photographic image analysis system, **nomela®**, using a modified iPad and proprietary software signal processing (the nomela® device). The software creates numerical values for several defined characteristics of the image some of which are not apparent to the naked eye.

(see section 4.3)

1.3.2 Early development of the technology accumulated information using library images of benign and malignant pigmented lesions against which thresholds were established to provide discrimination using a meta-engine.

(see Appendix A1)

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1.3.3 In the Moletest clinical study 004 the definitive diagnosis of lesions referred from primary care to specialist dermatologists as suspicious of melanoma/malignancy was used to determine the ranges of 5 signal processing parameters obtained from the images which enabled separation into two groups, N "not-at-risk" containing no cases of melanoma and R "at-risk" containing all the cases of melanoma; both groups contained benign lesions.

(see Appendix A2)

1.4 Summary of the clinical study C8

1.4.1 The nomela® technology is to be tested in this Study in secondary care by accumulating and analysing *in vivo* images of those pigmented skin lesions which are considered sufficiently suspicious to be referred by specialist dermatologist/plastic surgeon for biopsy/excision and histopathology. After a pilot phase of an initial 100 tests, the Study will involve testing 1200 to 2000 lesions such that completed tests on 200 melanoma have been accumulated.

1.4.2 The performance of nomela® will be assessed on all lesions tested by comparing the nomela® result (either "no evidence of melanoma" or "melanoma not excluded") with the subsequent confirmed diagnosis of "not-melanoma" or "melanoma" by histopathology.

(see Sections 4.2)

1.4.3 The ability to assign the lesions subjected to a nomela® test and subsequently confirmed as melanoma, to group R "melanoma not excluded" and by contrast not to group N "no evidence of melanoma" is to be evaluated.
Sensitivity and specificity of the nomela® test result for risk of melanoma will be determined. A high level of sensitivity is the objective.

(see 5.0)
(see 1.4.3 and Appendix A2)

1.4.4 During the Study a participant's inclusion will not influence clinical management. There will be no change to routine care except for the short time required for the nomela® test.

1.5 Parties to the Study and Agreements

For Agreements see separate documentation between the Parties:

- Moletest (Scotland) Ltd. SC478856
- Cambridge University Hospitals NHS Foundation Trust
- The University of Aberdeen

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2.0 OBJECTIVES

1. To measure the performance of the **nomela®** test as a risk calculator for melanoma in pigmented skin lesions of patients referred by specialists for biopsy/excision and histopathology.

2. To demonstrate that the nomela® test provides at least 95 ± 2 % sensitivity for not-melanoma.

3. To complete a Usability Assessment (as per requirements of the relevant regulation covering medical devices EN62366).

4. Subsidiary objective: to construct a Health Economics Technology Assessment, details of which are developed separately.

3.0 DESIGN

An open single-step non-randomised performance evaluation.

3.1 Subject inclusion criteria

3.1.1 Patients referred on routine clinical decision by the Dermatology/ Plastic Surgery Departments for biopsy/excision and histopathology of suspicious pigmented skin lesions including as possible melanoma.
3.1.2 Patients aged 16 years and over.
Patients with a prior history of skin cancer will be included.

3.2 Subject (lesion) exclusion criteria

3.2.1 Other skin conditions not considered to be pigmented moles.
3.2.2 Lesions not considered suitable for nomela®. (see 3.3)
3.2.3 Patients unable or unwilling to give informed consent.
3.2.4 Patients aged less than 16 years.

3.3 Prohibitions and restrictions

Lesions not considered suitable for nomela®:

pigmented moles smaller than 5mm diameter

moles obscured by hair or tattoos

moles in the mouth, eyelid, nailbed, genital and perianal areas

ulcerated lesions

non-pigmented moles which may be the amelanotic form of melanoma

lesions likely to be basal cell carcinoma, squamous cell carcinoma, Merkel cell tumours, lymphoma, metastatic carcinoma

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3.4 Screening tests

No screening tests form any part of this study.

3.5 Pilot phase

To provide reassurance that the nomela® software, defined after completion of study C7 and to be used by the nomela® device in C8, is performing technically as expected and reduce the risk of futile testing of up to 2000 participants, there will be an initial pilot phase of 100 tests.

If the observed rate of melanoma diagnosis in the pilot phase is found to be less than 1-in-12 (implying that more than 2400 lesions would need to be tested overall in the study at CUH to accumulate 200 melanoma) then the study would not continue at this site beyond the end of the pilot phase and alternative investigation sites would be sought.

3.6 Study duration

The duration for recruitment of patients in the study is envisaged to be 6 months. Scrutiny of histopathology records will extend for no more than 12 weeks beyond the end of recruitment.

3.7 Follow-up

No follow-up information is required for the study.

3.8 Discordance limits

To avoid futile continuation of the Study where the nomela® test is demonstrably not performing as expected the Study shall be discontinued if the following condition is satisfied: when the nomela® tests for 15 melanoma are discordant ie where the nomela® result has been given as "No evidence of melanoma”.

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4.0 Methods

4.1 The clinical visit

4.1.1 Referral for clinical photography prior to excision biopsy
All patients referred on routine clinical decision by the Dermatology/ Plastic Surgery Departments for biopsy/excision and histopathology of suspicious pigmented skin lesions including as possible melanoma which satisfy the inclusion and exclusion criteria and suitability for nomela® testing will be invited to participate.

(see 3.1, 3.2, 3.3)

The nomela® test is to be performed in clinic at the time of the standard photography. The Cambridge University Hospitals NHS Foundation Trust policy for use of a chaperone will be applied.
Operational aspects to minimise disruption to patient flow are considered.

4.1.2 Consent to participation
Following provision of an accessible copy (paper or electronic) of the Patient Information Sheet to eligible patients, and with appropriate opportunity for oral explanation if required, Consent to participation will be sought in the Dermatology/Plastic Surgery clinic.
An e-consent format will be used (see v2.3e).

(see NHS HRA/MHRA Joint statement on seeking consent by electronic methods)
https://www.hra.nhs.uk/documents/1588/hra-mhra-econsent-statement-sept-18.pdf
(see Participant Information Sheet and Consent Form in separate documentation)

Withdrawal of consent: At the patient's request subsequent withdrawal of consent will be documented by a record of such withdrawal (date, mode of communication, name and signature of physician/nurse) attached to the original signed consent both of which are retained. The Clinical Research team must be advised of such withdrawal by email and will confirm removal from the Study by email to the Principal Investigator and the Sponsor. Following Withdrawal of Consent all information obtained during the nomela® test is deleted from the information stored and no use of the information is made.

4.1.3 The nomela® test
The nomela® test will be performed by the trained operator (clinical research nurse) under the supervision of the Media Studio using the designated nomela® device provided for the Study by Moletest (Scotland) Ltd.
The time required for the test including identification, image acquisition and generation of test result should be 3 - 5 minutes (but less with experience).

(see 4.3 for technical aspects)

4.1.4 Failure to complete a nomela® test

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A list will be kept of pigmented moles sent for routine medical photography by the specialist in which the nomela® test was attempted but not completed with the reason for non-completion.

4.1.5 Biopsy/excision and histopathology
The procedure for biopsy/excision and handling of tissue samples will follow the recognised practice at Cambridge University Hospitals NHS Hospitals Trust including written information and consent, preparation, documentation, sample identification and transfer to the Dept. of Pathology.
The Dept. of Pathology confirms following current national guidelines for reporting and of the retention/discard of tissue and prepared samples.

4.2 Technical aspects of the nomela® test

4.2.1 Equipment
Moletest (Scotland) Ltd. will provide the nomela® devices (modified Apple iPad) to the designated authorised personnel as follows:

Medical Illustration: to be used for supervising the nomela® test.
(see 4.2.2 - 4.2.7)
Clinical Research: to be used for the nomela® test and for access to the Study Log.
(see 4.2.5 and 4.3)

4.2.2 Training of operators
Training in the use of the nomela® test is considered essential although the nomela® test is intuitive and brief. A short Training Programme is available for all prospective operators. Training will be provided by Moletest (Scotland) Ltd. and satisfactory completion of training will be recorded in a Training Log.
(see nomela® Screening Device Training Plan available separately)

4.2.3 Conducting the nomela® test
The nomela® test follows a predetermined sequence. Authorised users log in. Date, time and place are recorded automatically. Patient identification is obtained by scanning, in this Study, of the hospital number.
The Participant number is generated automatically in this Study by the nomela® test. The string of the number allows for multiple lesions in one participant with a distinct digit for each lesion. In effect this is a combination participant-lesion number.
Location of the lesion is recorded in the nomela® test by regional and close-up images. This information may be used to correlate location information recorded by clinical correspondence and histopathology reports.

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The close-up image is cropped manually by the operator to obtain optimal perimeter recognition and then accepted.

The nomela® test reference
A unique anonymised label, the nomela® reference, is generated randomly and automatically for each lesion during the nomela® test as a 128-bit number "universally unique identifier" (UUID) which is shown on the report page as a 2-dimensional QR code. This information will be inserted into the Study Log but is not required by the operators and clinical research team.

Tests on additional lesions which satisfy the Study criteria may be made in the same or different region each labelled by a separate nomela® test reference.

(and see section 4.3.5)

Unsuitable images: The nomela® test has been designed to reject any images of skin lesions that are unsuitable for analysis either because of an uncertain border or because they are too small (less than 7000 data points per image). The number of such lesions which do not satisfy these capture criteria will be recorded.
Standardisation of lighting: Images are captured using available light. Any lighting should be diffuse and the source (window or ceiling lights) should be at least 2 metres away to avoid any flare on or around the lesion.
Positioning of device and lesion: The nomela® device should be positioned to obtain a sharp focussed close-up image, on a plane parallel with the lesion, with neither a requirement for varied angles nor cross lighting.

(see separate document: Instruction for nomela® test image capture)

4.2.4 The nomela® analysis software

The nomela® test incorporates specific software for image analysis based on signal processing. This is not a machine-learning/neural network/AI system.
The Build version of the proprietary nomela® software to be tested in this clinical study will be nomela® 2 incorporating the iPad number and the iOS version.
After the pilot phase, the software will not be modified during the Study.
The software cannot be influenced by the operator.
For this Study the Result page and Report page generated by the nomela® test will not be available to the operator.

4.2.5 The nomela® test result

The nomela® software recognises the perimeter of the lesion from the close-up cropped image. Using non-scalar metrics of the image within the recognised perimeter and a combination algorithm of 5 predefined parameters a score is obtained. Based on the score the nomela® test assigns the lesion either to "no evidence of melanoma" (group N) or to "melanoma not excluded" (group R). Both groups contain benign lesions but group N should contain no melanomata.

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All information from the test is transferred automatically to the Study Log. Completion of the nomela® test is normally shown on the device by a Result page. For this Study the result will not be available to the operator and research team but will be passed to the medical statisticians.

4.2.6 Transfer, storage and retrieval of test information
Secure approved 4G connection enables uploading of the test information to secure approved storage.
No patient information or test information is retained on the nomela® device after this secure transfer.
(see Statements on Data Handling and Information Governance, Appendix D)

4.2.7 Usability Assessments
Usability Assessments of the nomela® device and test will be obtained from investigator operators to satisfy regulatory requirements for medical devices in development. Forms for this purpose will be provided.
(see Appendix B3)

4.3 Clinical data collection

4.3.1 Clinical data collection
The Study nomela® C8 is designed to eliminate paper case record forms and paper participant log. The nomela® test is electronic and is designed to eliminate transcription errors: the Patient(Participant) information, as hospital number, is captured by scanning at the start of the nomela® test. A cumulative Study database is populated automatically in a secure system. This information (except for the Result) is available to the authorised specialists and clinical research team accessible by approved systems.
(see 4.2.3)
(see Statement on the handling of Data, Appendix D)
The (only) further information required for the Study is the histopathology diagnosis. This information is obtained from the Dept of Histopathology/ EPR by category by authorised personnel from Clinical Research/ Dermatology/Pathology requiring manual entry to the Study database.
(see 4.3.4)

4.3.2 Participant Information Sheet and Consent Form
Copies of the Participant Information Sheet and the completed e-Consent Forms will be stored securely for all participants at the Investigator site for subsequent central storage and archive by the Cambridge University Hospitals NHS Foundation Trust.

4.3.3 The Study Database
The Study database will be populated by the nomela® output with the authorised user name/identifier, test date, time, place, hash-encrypted-

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hospital-number, participant-lesion number, test images, nomela® reference, test result.
For addition of the code for the histopathology diagnosis category:
see 4.3.4.
For details of encryption and transmission/storage:
see separate AppendixD1(2019b) including flow diagram
The List of lesions tested by nomela® in the study period will be accessed by agreed process for the Department of Dermatology and Clinical Research.
Identification of Cases which were tested by nomela® in the Study will be independent of Moletest (Scotland) Ltd.

4.3.4 Identification of diagnoses and Categorisation of Cases
Accurate identification and linkage of (a) patient, lesion, nomela® test reference of image and result with (b) patient-lesion histopathology report is crucial. The nomela® test includes accurate location visual information to aid this process.

The histopathological diagnosis will be collected by Clinical Research/ Dermatology from the Department of Pathology, Cambridge University Hospitals NHS Foundation Trust of those lesions completing the nomela® test.

Manual entry of lesion diagnosis
The Study Log holding the Participant-Lesion Number and hospital number will allow manual interpolation of the histopathological diagnosis by category. The following categories of diagnosis will be used:

1 not melanoma
2.1 melanoma-in-situ (including lentigo maligna and acral lentiginous melanoma-in-situ)
2.2 melanoma superficial spreading
2.3 nodular melanoma
2.4 lentigo maligna melanoma
2.5 acral lentiginous melanoma
2.6 melanoma indeterminate
2.7 melanoma not otherwise defined
3 uncertain diagnosis
9 no information available/no biopsy

Time limit
A time limit of 12 weeks from the end of the recruitment period will be set for the acquisition of histopathology diagnoses.

4.3.5 Case Lists
List of Cases
The List of Cases generated from the Study database will show:
Participant-lesion number (maximum of 9 lesions per participant)
Hospital number

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Diagnostic category (histopathology)

(see 4.3.4 and Appendix C1)

Abbreviated List of Cases

The Abbreviated List of Cases generated from the Study database will show:

Participant-lesion number
Diagnostic category (histopathology)
nomela® test result

forming the Study Database for statistical analysis for forwarding to the University of Aberdeen.

(see Appendix C2)

Lesions confirmed as melanoma during the Study period but which were not submitted to the nomela® test do not form the Cases for the Study.

4.4 Information security, transfer, retention and governance

4.4.1 Security of the nomela® device and data transmission to the Study database

NHS approved security will have been obtained for use of the nomela® device and for transmission of nomela® test data to the Study database.

After upload no images or other patient information are retained on the nomela® device. The only information held long-term on the nomela® device is the unique identifier for that iPad, the nomela® test software and the authorised user list for that nomela® device.

(see separate Statement from Moletest (Scotland) Ltd. on Data Handling and Information Governance and flow diagram)

4.4.2 Retention of study information

4.4.2.1.At the time of upload to the Study database the following information will be transferred securely to Moletest servers located in the UK: the nomela® device identifier, the authorised user for that test, the date of the test, the hash-encrypted-hospital number, the participant-lesion number, the test images, nomela® reference, raw data (5 parameters) and test result.

4.4.2.2 After upload to the Study database of the histopathology diagnosis the hash-encrypted-hospital-number will be automatically deleted so that retained information is without patient identifiable information.

4.4.2.3 Where no histology diagnosis has been discovered and entered to the database at 12 weeks after the nomela® test the hash-hospital-number is expunged automatically from the Moletest database.

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4.4.3 Information Governance

Moletest (Scotland) Ltd. recognises the importance of the highest standards for information governance.

The pathway to, location of and security of, the servers are described in the Statement on Data Handling Moletest (Scotland) Ltd. and Information Governance Flow Diagram.

(see separate documentation: Appendix D)

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5.0 Statistical Considerations: Sample size and Statistical Analysis

Study Cases require both prior nomela® test result and diagnosis confirmed by histology of "not-melanoma" or of "melanoma".

5.1 Sample size:

For this Study a total sample generating a minimum of 200 confirmed melanoma Cases will be evaluated. Of those lesions referred for histology by the Department of Dermatology it is estimated that from 1 in 6 up to 1 in 10 are found to be melanoma and thus approximately 1200 to 2000 lesions will be tested.

5.2 Statistical analyses:

5.2.1 Cases for the Study are defined as those cases of pigmented cutaneous moles referred for biopsy/excision by the dermatologist/plastic surgeon which satisfy the inclusion and exclusion criteria and are suitable for nomela® testing.

(see 3.1 - 3.3)

The data-set required for performance analysis will be:

the total number of nomela® tests performed during the study
the number of tests excluded
the number of tests assigned to "no evidence of melanoma" (group N)
the number of tests assigned to "melanoma not excluded" (group R)
the number of not-melanoma cases in group N
the number of melanoma cases in group N
the number of not-melanoma cases in group R
the number of melanoma cases in group R

5.2.2 Outcome measures
Primary outcome measure: sensitivity (95 % CI) of the nomela® test for not-melanoma.
Secondary outcome measure: the proportion (95% CI) of lesions that the nomela® test finds as having 'no evidence of melanoma'.

5.2.3 The distribution of the nomela® test results between group N and R (see 1.4.3 & 3.6.2) for the Cases will be calculated. Estimates of sensitivity, specificity, positive and negative predictive values, and likelihood ratios (with 95% confidence intervals) will be calculated.

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6.0 ADVERSE EVENTS REPORTING AND SAFETY REVIEW

6.1 Adverse Events are considered highly unlikely in this study and therefore it is not intended to collect information on adverse events on a routine basis nor conduct a Safety Review.

6.2 Safety issues are as associated with the use of any Apple iPad for taking photographs. There is no direct contact of the device with the study patient.

6.3 Safety review is not considered to be required since clinical management is not affected by acquisition of a nomela® test result.

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7.0 REGULATORY ASPECTS; CLINICAL RESEARCH ETHICS REVIEW; MONITORING; ARCHIVE

Moletest (Scotland) Ltd. aims to adhere to ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice.

7.1 Protocol registration

Moletest (Scotland) Ltd has obtained a Protocol Registration System account (organisation name: Moletest; administrator username Dr P S Freedman) with NIHR Clinical Research Network(CRN) Central Portfolio Management System (CPMS) to register nomela® Clinical Study C8 in anticipation of adoption to the NIHR Portfolio.

see supportmystudy@nihr.ac.uk

If not adopted, the Study Protocol C8 will be registered on the ISRCTN database.

see https://www.isrctn.com/

The Principal Investigator is Dr Nigel Burrows, Consultant Dermatologist, Cambridge University Hospitals NHS Foundation Trust and Co-Investigators are Dr Ed Rytina, Consultant Pathologist, Cambridge University Hospitals NHS Foundation Trust and Mr Jeremy Nayler, Head, Media Studio, Cambridge University Hospitals NHS Foundation Trust.

7.2 Medicines and Healthcare Products Regulatory Agency (MHRA)

The Moletest™ software technology has CE marking, under the Medical Devices Regulations 2002: regulation 19, as a Class I Device and specified as a dermatological differential (calculator) diagnostic aid. Notification was issued by MHRA dated 14 May 2014 reference CA014191.

see
CA014191 Moletest UK Ltd. Letter from MHRA dated 2014
MHRA 4407 Medical Device Registration for Moletest (Scotland)- current
Notify MHRA about a clinical investigation for a medical device- current

7.3 Clinical Research Ethics Committee review

The Clinical Study Protocol and related documents will be submitted through IRAS for review and approval by an independent NHS Clinical Research Ethics Committee.

Any change of study protocol if significant and deemed necessary by the Principal Investigator(s) or by the Sponsor will be reported to the Clinical Research Ethics Committee in writing, and agreement obtained before implementation.

7.4 Study monitoring

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Monitoring will be the responsibility of Moletest (Scotland) Ltd.

7.5 Study data archive

All data will be held securely after completion of the Study according to ISO 14155:2011.

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8.0 Responsibilities, Report and Quality Assurance

Project Director - Mr Bruce Murray: ensuring relevant approvals and agreements are obtained; co-ordinating technical aspects of the study including e-output from nomela® to Cambridge University Hospitals NHS Foundation Trust EPR systems and other data storage systems.
Data Protection Officer (DPO), Moletest (Scotland) Ltd.

Study Director - Dr Peter Freedman: co-ordinating the outline clinical study plan; preparation of the Clinical Study Protocol in consultation with the Project Director, Principal Investigator(s), Investigators, Medical Statistics Team and Consultants to Moletest (Scotland) Ltd.; overseeing the conduct and reporting mechanism; preparation of the Report in consultation with the Project Director, Principal Investigator(s) and Medical Statistics Team; preparation of a paper for submission to a peer-reviewed journal in consultation with the Principal Investigator and (D J) Statistics Team.
Caldicott Guardian, Moletest (Scotland) Ltd.

Principal Investigator - Dr Nigel Burrows: scientific, clinical and ethics review of the aims of the study encapsulated in the study protocol; facilitating and providing information on the dermatology records of the cases referred as per protocol; advice on preparation of the Report; co-authoring of a paper for submission to a relevant peer-reviewed journal with Moletest Medical Director and with assistance from Moletest Technical Director and the Medical Statistics Team.

Co-Investigator - Dr Ed Rytina: scientific, clinical and ethics review of the aims of the study encapsulated in the study protocol; facilitating access to and providing information on the histopathology reports of the cases referred for biopsy/excision- as per protocol in Cambridge University Hospitals NHS Foundation Trust; advice on preparation of the Report; co-authoring of a paper for submission to a relevant peer-reviewed journal with Moletest Medical Director and with assistance from Moletest Technical Director and the Medical Statistics Team.

Co-Investigator - Mr Jeremy Nayler: supervising the deployment of the nomela® test in the dermatology/plastic surgery clinic as per protocol in Cambridge University Hospitals NHS Foundation Trust; advice on preparation of the Report; co-authoring of a paper for submission to a relevant peer-reviewed journal with Moletest Medical Director and with assistance from Moletest Technical Director and the Medical Statistics Team.

Head, Medical Illustration, Moletest (Scotland) Ltd. - Mr Ross G Milligan: providing and supporting training of clinicians and medical photographers

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in the use of the iOS device with embedded nomela® technology; advice on integration into NHS EPR systems.

Head, Information Technology, Moletest (Scotland) Ltd. - Mr Nick Ager: programming development; co-ordinating technical aspects of electronic data transfer, storage and retrieval.
Senior Information Risk Owner (SIRO), Moletest (Scotland) Ltd.

Medical Statisticians (Prof. Amanda Lee): providing advice on the design of the study and analytical methodology; commenting on the study protocol and IRAS form; providing a report with results of the statistical analysis. Assisting the Study Director and Principal Investigator in the preparation of a paper for submission to a peer-reviewed journal.

Regulatory Affairs and Quality Assurance Representative {tbd}: ensuring that testing, reporting and all appropriate procedures are documented in accordance with the requirements of the Protocol and relevant Appendices as approved by Clinical Research Ethics Committee(s) and Regulatory Agencies and under relevant regulations for medical devices {Emergo}.

9.0 HEALTH ECONOMICS TECHNOLOGY ASSESSMENT

Health economic technology assessments have been commissioned to support the economic case for active deployment of nomela®.

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APPENDIX A1&2
Moletest Ltd. reports to date

APPENDIX A1
Library-image based data

Summary of REPORT-007
Using library images of 43 benign, 44 dysplasia and 35 melanoma lesions, REPORT-007 shows that, as a result of improvements in identification to earlier algorithms regarding the perimeter of the lesion and effective filtering of unsuitable images, there were no outliers - i.e. the ranges for each condition were well defined and the App should not generate any missing values (Murray,B on file Moletest (UK) Ltd. Quality Management System).

APPENDIX A2
MOLETEST004 CLINICAL STUDY

SUMMARY

i) The performance of the Moletest™ technology (**nomela®**) was evaluated to assess its capability of discriminating pigmented skin lesions as benign from among those considered suspicious of skin malignancy including melanoma. The clinical study Moletest004 (NHS Lanarkshire L14100) (IRAS project ID: 159049) was approved by the NHS Research Ethics Committee, Cambridge South (15/EE/0097).

ii) A total of 1200 participants were recruited in hospitals in Lanarkshire, Scotland over a 12 month period starting in April 2015 in people referred from primary care for specialist dermatology review of suspicious pigmented moles. Recruitment followed presentation of a Participant Information Sheet and provision of written informed consent. The photographic images were taken by the Medical Illustration Service, using a dedicated iPad Air2 loaded with the **nomela®** technology. The study was managed by the Clinical Research Nurse team for NHS Lanarkshire for Dr Girish Gupta, Lead Skin Cancer Specialist.

iii) In the calibration phase the number of participants with eligible lesions was 381 and the number of eligible lesions was 447. One participant withdrew from this phase of the study. The calibration phase was used for refining the app user interface and improving technical aspects of image capture but not changing the underlying algorithms. The statistical analysis of the calibration phase was used to establish the usefulness of the methods employed.

iv) In the validation phase from 13 August 2015 to 25 April 2016 the number of participants recruited was 795. There were no patient

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withdrawals. From 911 lesions some 715 were suitable for final analysis after 196 exclusions, some dual, for unmatched uploaded images (19), unsuitable images on inspection (95), unreturned biopsy results (6), unavailable final diagnosis (48) and incomplete valid measurements (35).

v) Considering the 715 lesions which have usable images, available diagnoses and all 5 proprietary signal processing measurements, 61.1% had at least one measurement beyond the range for ‘melanoma' (D1). Of these 437 lesions, 346 were benign [79.2%], 59 dysplasia [13.5%] and 32 [7.3%] other malignancies.

To use the D1 discriminator would mean over 60% of lesions otherwise unassessed could exclude melanoma. In this discriminated group (N) about 80% are benign with about 13% dysplasia and 7% non-melanoma malignancy.

vi) When comparison is made beyond the range for 'melanoma or other malignancies' the discrimination (D2) may be more useful but is less powerful at 23.9% of lesions. Of these 171 lesions, 140 were benign [81.9%] and 31 dysplasia [18.1%].

To use the D2 discriminator would mean about 24% of lesions otherwise unassessed could exclude melanoma and all other skin malignancies. In this discriminated group (N) about 82% are benign with about 18% which are dysplasia irrespective of grade.

vii) A further revision of the range for each measurement for melanoma-and-other-skin-malignancies to include approximately 90% of dysplastic lesions (D3), resulted in 18.0% of all lesions having at least one measurement beyond this range. Of these 129 lesions, 113 were benign [87.6%] and 16 were dysplastic [12.4%].

To use the D3 discriminator would mean about 18% of lesions otherwise unassessed could exclude melanoma and other skin malignancies and most dysplasias. In this discriminated group (N) about 88% are benign with 12% which are dysplasia irrespective of grade.

viii) Thus, in pigmented moles referred as suspicious of melanoma including other malignancy in this Study, after excluding 196 lesions for clinical, technical or data capture reasons, and using the 715 lesions with all 5 signal processing parameters available, **nomela®** was able to exclude melanoma, by using discriminator D1, in 61.1% of lesions.

Further **nomela®** was able to exclude melanoma and other skin malignancy, by using discriminator D2, in 23.9% of lesions or, alternatively to exclude melanoma and other skin malignancy and 90% of dysplasia, by using discriminator D3, in 18.0% of lesions.

Using D1 the low risk group (N) contains 79.2% which are benign, 13.5% which are dysplasia and 7.3% other non-melanoma malignancy. Using D2, the low risk group (N) contains 81.9% benign and 18.1% dysplasia. Using D3, the low risk group (N) contains 88% benign and 12% dysplasia.

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ix) The principal aim of the technology is to provide a diagnostic aid to screen out, with sufficient confidence, lesions which are NOT melanoma. The cutaneous dysplasias are not life threatening and the majority require no treatment. Basal cell carcinoma is almost exclusively localised and slow-growing. Squamous cell carcinoma only rarely metastasises and is slow-growing. The results here suggest that it is possible, using the D1 discriminant, to exclude the potentially life-threatening melanoma in at least 60% of presenting lesions.

Increasing the discrimination performance leads to a smaller proportion of the total presenting for assessment which the technology separates into a low risk group. If it is deemed necessary to exclude all skin malignancies including melanoma it appears that the performance using D2 as discriminant function might also be considered useful and which is applicable to just under one-quarter of the total lesions presenting for assessment.

x) The clinical utility of **nomela®** on the basis of this evidence is that, with the cautions regarding relatively low absolute numbers of malignancies including melanoma in this study, it should be possible to deploy the technology in trained professional hands to assist in the diagnosis of pigmented moles. This may reduce the need for specialist review who are currently referred by 50-60%, with appropriate advice and caution. If this enables the services in primary and specialist care to focus efforts then this should lead to clinical and economic benefits. Further refinement of the **nomela®** technology will seek to shift the ratios to those which are even more useful.

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APPENDIX B1, 2 & 3
Participant Information Sheet; Consent Form; Usability Assessment Form

APPENDIX B1
Participant Information Sheet

see separate documentation

APPENDIX B2
Consent Form

see separate documentation

APPENDIX B3
Usability Assessment Form

see separate documentation

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APPENDIX C1&2

Items for
List of Cases and Abbreviated List of Cases

APPENDIX C1 List of Cases at NHS site

Hospital number

Participant-lesion number

Diagnostic category (histopathology)

1 not melanoma
2.1 melanoma-in-situ (including lentigo maligna and acral lentiginous melanoma-in-situ)
2.2 melanoma superficial spreading
2.3 nodular melanoma
2.4 lentigo maligna melanoma
2.5 acral lentiginous melanoma
2.6 melanoma indeterminate
2.7 melanoma not otherwise defined
3 uncertain diagnosis
9 no information available/no biopsy

APPENDIX C2 Abbreviated List of Cases transferred to Medical Statistics, University of Aberdeen

Participant-lesion number

Diagnostic category (histopathology)

1 not melanoma
2.1 melanoma-in-situ (including lentigo maligna and acral lentiginous melanoma-in-situ)
2.2 melanoma superficial spreading
2.3 nodular melanoma
2.4 lentigo maligna melanoma
2.5 acral lentiginous melanoma
2.6 melanoma indeterminate
2.7 melanoma not otherwise defined
3 uncertain diagnosis
9 no information available/no biopsy

nomela® test result.//

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APPENDIX D1&2
Data handling and governance

APPENDIX D1

Statement by Moletest (Scotland) Ltd. on Data Handling (2019b_C8)

Please see Appendix D1 (2019b) submitted separately

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nomela® C8 Schedule of Events

step	activity	per participant in secondary care				
		lesion1	(lesion2 if present)	(lesion3 if present)		
	visit	1	1	1		
1	**inclusion criteria**	*	*	*		
1	**exclusions**	*	*	*		
2	**Participant Information Sheet**	*				
3	**Consent Form**	*				
4	**nomela® test (1 - 3 minutes per lesion)**	*	*	*		
5	**check test is uploaded**	*	*	*		
6	**check receipt of email (e-consent/hospital number/participant number)**	*	*	*		
7	**search histology diagnosis (pathology/ dermatology) by EPR/ paper records**	*	*	*		
8	**add histology diagnosis to database (see Appendix C1&C2)**	*	*	*		
9	**confirm Abbreviated List of Cases (see Appendix C1&C2)**	*	*	*		

APPENDIX E

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REFERENCES AND ATTACHMENTS

References

Revised U.K. Guidelines for the management of melanoma 2010 British Association of Dermatologists, British Journal of Dermatology (2010) **163**, 238-256

NICE Guidelines: Skin Cancer (22/08/2017) https://pathways.nice.org.uk/pathways/melanoma

NICE Guidance: Melanoma assessment and management [NG14] (2015) http://bit.ly/2sdpnjW or https://www.nice.org.uk/guidance/guidance/ng14

Cancer Research UK www.cancerresearchuk.org

US National Cancer Institute: General information about melanoma (2014)

Clinical investigations of medical devices- statistical considerations Medicines and Healthcare Products Regulatory Agency

European Commission Guidelines on Medical Devices Clinical Evaluation MED DEV 2.7/1 revision 4 (June 2016) eu-meddev-2_7_1-clinical-evaluation-guide-for-manufacturers-and-nb or https://www.gov.ukgovernment/uploads/system/uploads/attachment_data/file/138296/dh_103653_1_.pdf

Usability Standard IEC/EN62366-1 (2015) http://www.iso.org

UK Guidance on the use of mobile photographic devices in Dermatology (2017 July)

Joint statement on seeking consent by electronic methods v1.2 (September 2018) MHRA/ NHS HRA et al.
www.gov.uk/hra-mhra-econsent-statement-sept-18.pdf

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ATTACHMENT 1

Skin cancer statistics | Cancer Research UK
www.cancerresearchuk.org/health-professional/cancer-statistics/statistics.../skin-cancer searched 2017nov

Incidence of cutaneous melanoma The crude incidence rate shows 24 new melanoma skin cancer cases for every 100,000 males in the UK and 24 for every 100,000 females.

The European age-standardised incidence rates (AS rates) for males are significantly lower in Northern Ireland compared with other UK countries while for females, the rate is significantly lower in Scotland compared with England. Rates do not differ significantly between the other constituent countries of the UK for either sex.

Mortality from malignant melanoma trends
Malignant melanoma is the 17th most common cause of cancer death in the UK (2014), accounting for 2% of all cancer deaths.
In 2014, there were 2,459 malignant melanoma deaths in the UK: 1,431 (58%) in males and 1,028 (42%) in females, giving a male:female ratio of around 14:10.The crude mortality rate shows 5 malignant melanoma deaths for every 100,000 males in the UK and 3 for every 100,000 females.

The European age-standardised mortality rates (AS rates) do not differ significantly between the constituent countries of the UK for either sex.

Malignant melanoma mortality rates have increased by 156% in the UK since the early 1970s.

The European Age-Standardised (AS) mortality rates between 1971-1973 and 2012-2014, increased for males by 237% and for females by 89% in this period.

AS mortality rates in the UK between 2003-2005 and 2012-2014 for malignant melanoma have increased by 15% for males and females combined, with a larger increase in males (20%) than in females (8%).

In England (2007-09), cutaneous melanoma age standardised incidence rates for males and females were 16.6|17 per 100,000 respectively. Tumour thickness data showed (2007-09) that in 45% of males | 53% of females tumours were thinner than 1mm (T1). Thicker tumours of 1.01-2mm (T2), 2.01-4mm (T3) and >4mm (T4) were observed in 22%, 19% and 14% of males, and 21%, 15% and 10% of females respectively. In addition 4% of cases under 50 years old were T4 compared with 14% of 50 years old and over.

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Malignant Melanoma Standardised Mortality Rates (SMR) and Age Standardised Mortality Rates (aSMR) by Strategic Health Authorities in England showed a variation in mortality across England and between males and females. The average SMRs in England (2008-10) for males and females were 3.1 v 2.0 per 100,000 respectively.

The average aSMR per 100,000 population for malignant melanoma (England 2008-2010) in all 10 strategic health authorities was male 3.2 and female 2.05.

(drawn from Public Health England NCRAS ncin.org.uk (National Cancer Intelligence Network)

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