Clinical Investigational Plan

Investigational Medical Device	Dermalyzer
Investigation code	AI-DSMM
CIP Version	3.0
Date	21Mar2022
CIV-ID	CIV-21-12-038346

TITLE OF THE CLINICAL INVESTIGATION

A prospective clinical investigation to assess the diagnostic precision of the AI tool Dermalyzer to identify malignant melanomas in subjects seeking primary care for melanoma-suspected *cutaneous* lesions

Investigation Design *

A pre-market, prospective, confirmatory, first in clinical setting, pivotal multi-centre, non-interventional clinical investigation to evaluate the clinical safety, performance and benefit of Dermalyzer in patients with cutaneous lesions where malignant melanoma cannot be ruled out.

Indication studied*

Malignant Melanoma

Investigational Medical Device

Dermalyzer

Device classification

II b

Comparator product

Not applicable

Duration of intervention

Feb2021-

Sep2022

Sponsor signatory

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The Karolinska Institutet (KI) and Region Östergötland (RÖ) share the sponsor responsibilities for the clinical investigation and collaborate with each other to conduct the clinical investigation. For the submission the Region Östergötland and Magnus Falk will be listed as the sponsor and National Coordinating Investigator (NCI). Magnus Falk and Panos Papachristou are both the Principal Investigators (PI) for each region and the 30 sites listed under them in their and adjacent regions. A list of investigators and staff at each site will be archived in the files at the Sponsor and at the site.

* *if not apparent from the title*

The following amendments have been made to the Final CIP Version 1.0; 2021-12-23

Amendment No.	**Date of Amendment**	**Revised CIP Version**
1.0	*09Feb2022*	*2.0 updates made based on comments from the Competent Authority*
2.0	*21Mar2022*	*3.0 updates made to the version number of Dermalyzer and update to the dermatoscopes to use*

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3 SYNOPSIS

Title of the clinical investigation A prospective clinical investigation to assess the diagnostic precision of the artificial intelligence (AI) tool Dermalyzer to identify malignant melanomas in subjects seeking primary care for melanoma-suspected *cutaneous* lesions		
Investigation code AI-DSMM	**Investigational Medical Device** Dermalyzer	**IMD classification** IIb
Intended use Dermalyzer is a device intended to be used as a decision support system for assessing cutaneous lesions suspected of being melanomas. The input from the device is not intended to be used as the sole source of information for diagnosis. The device should be used in combination with a medical professional assessment of the suspected lesion. Intended to be used by medical professionals. The service does not provide any other diagnosis.		
Coordinating/Principal Investigator Magnus Falk, *MD, assoc.professor,* Region Östergötland		
Time period for the clinical investigation Estimated date of first subject enrolled: Q1 2022 Estimated date of last subject completed: Q3 2022		
Design of the clinical investigation This will be a pre-market, prospective, confirmatory, first in clinical setting, pivotal multi-centre, non-interventional clinical investigation to evaluate the clinical safety, performance and benefit of Dermalyzer in patients with cutaneous lesions where malignant melanoma (MM) cannot be ruled out.		
Objectives and endpoints <u>Primary objective</u>		

The primary objective of the investigation is to determine the diagnostic precision of the device; to answer at which level the AI tool Dermalyzer can identify malignant melanomas among cutaneous lesions that are assessed in clinical use due to any degree of malignancy suspicion.

Primary endpoint

The primary endpoint will be measured as the true proportion; by testing if the device based on AI gives correct results as compared with the result of the lesion analysis (the final classification by histopathology (PAD) in at least a certain proportion (π) of the analyses.

Secondary objectives

As secondary objectives a number of analyses will be done.

To evaluate usability and applicability in clinical praxis of Dermalyzer by users (medical professionals)

To gain an increased knowledge and understanding of how digital tools enhanced co-artificial intelligence can assist physicians with the right support for an earlier diagnosis of malignant melanoma.

Secondary endpoints

User questions including System Usability Scale to evaluate the usability and applicability in clinical praxis.

Exploratory objective

To explore health economic aspects of improved diagnosis support

Exploratory endpoints

Collecting health economic related information by survey to participating sites

Number of subjects planned

The estimated number of lesions to be recruited is approximately 500 in order to evaluate 239 eligible lesions, based on power/sample size calculation.

Diagnosis and main eligibility criteria

Inclusion criteria:

1. *Patients ≥18 years*
2. *Patients attending a primary care facility with at least 1 suspicious skin lesion where MM cannot be ruled out.*
3. *Willingness and ability to provide informed consent.*

Exclusion criteria:

1. *Cutaneous lesions that are considered as benign by the investigator and thus not subject for further clinical investigation*
2. *Cutaneous lesions in areas that are not suitable for dermoscopy imaging*
3. *Cutaneous lesions in areas with any form of scarring of tissue due to injury*
4. *Damaged or injured non intact skin where the cutaneous lesion is located*
5. *Individuals with skin type V and VI according to the Fitzpatrick scale (darker brown or black coloured skin)*
6. *Cutaneous lesions in areas covered by tattoos*
7. *Cutaneous lesions in abundantly hairy skin areas (provided the the area cannot be shaved freely from the hair to allow clear view for the dermatoscope)*
8. *Images where the entire lesion is not inside the photo*
9. *Images that are out of focus*

Methodology

The subjects will be included from around 30 primary care centres in Sweden. If the subject's lesion(s) is suspected of melanoma or melanoma cannot be ruled out, the subject is asked to participate in the investigation.

The investigator examines the subject's lesion(s) and makes the clinical assessment of the subject lesion(s) based on established clinical decision algorithms (such as "Chaos & clues", "3- or 7-point checklist", or the ABCDE concept) of whether there is a suspicion of MM, according to the usual clinical routine (also includes very low suspicion of MM but cannot be completely dismissed). The investigator takes dermoscopy images according to standard of care and archives the image(s) according to clinical routine. The investigator decides on action, based on his or her MM suspicion (excision at the primary care centre or referral for excision or referral to a dermatologist for further

assessment). If the subject has agreed to participate in the investigation, the investigator indicates in the CRF the clinical suspicion level of MM, and decided action.

The investigator takes images of the lesion(s) again, this time with a mobile phone, containing the IMD AI SW, connected to a dermatoscope, and follows the on-screen instructions. The image is processed by the AI SW and the results are visible on the screen within seconds. A unique auto generated code number is also presented. The code number is registered on the enrollment log and in the CRF. The investigator records how he considers that the degree of suspicion of MM (higher vs lower) would have been affected by the AI SW result if it had been the governing body for the treatment.

When the subject has been fully examined and receives the final tumor diagnosis from the histopathology/PAD results (melanoma/non melanoma), the degree of agreement between the PAD and the outcome of the AI SW decision support is calculated with the Kappa-analysis and the diagnostic accuracy to be able to distinguish melanoma from non-melanoma in the form of sensitivity and specificity as well the positive and predictive value. The corresponding comparison is performed from the examining investigators' estimated clinical degree of suspicion, as well as the diagnostic accuracy when both the PAD and the AI decision support are weighted together (i.e. in cases where the investigator and the decision support are in agreement in their assessment). The clinical investigation will collect information from the users, how participating users (investigators at the site) experience the usability of the AI SW decision support and attaching applications, from short surveys including the validated System Usability Scale.

Use the same overall description given in Section 9.1.

Duration of exposure to the Investigational Medical Device

The subjects will not be in any direct contact with IMD Dermalyzer.

Duration of subjects' involvement in the investigation

The subjects will only perform 1 visit at a primary care centre to assess the cutaneous lesion(s).

Clinical performance assessments

The subject will be examined according to clinical routine. The cutaneous lesions where MM cannot be ruled out (study lesions) will be photographed with a digital dermatoscope. The digital image will then be able to be instantly uploaded to the study's AI enhanced web application (Dermalyzer), where the AI algorithm performs the image analysis within a few seconds.

Clinical safety assessments
All considered reportable events in accordance with MDR, will be captured. The subject included in the investigation will follow the standard of care. The use of the AI will not influence the subject or the medical care of the subject.
Statistical methods The sample size of at least eligible 239 lesions is calculated by an expected true proportion of 95% with 80% power. The estimated frequency of actual found malignant melanoma is 4.65% (or 12 MM out of 239 lesions).

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
AE	Adverse Event
ADE	Adverse Device Effect
AI	Artificial Intelligence
AIMT	AI Medical Technology AIM AB
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigational Plan
CRF	Case Report Form
DD	Device Deficiency
EEA	European Economic Area
FAS	Full Analysis Set
ICF	Informed Consent Form

IEC	Independent Ethics Committee
IFU	Instructions for use
GCP	Good Clinical Practice
IMD	Investigational Medical Device
MM	Malignant Melanoma
MDSW	Medical Device Software
N/A	Not applicable
PAD	Pathological Anatomical Diagnosis
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

Enrolled subject	Subject who has signed the Informed Consent Form (ICF)
Screen failure	Enrolled subject not included
Included subject	Subject fulfilling the eligibility criteria
Withdrawn subject	Subject included but not completed

Completed subject	Subject completed the investigational period, including follow-up

5 ETHICAL AND REGULATORY REQUIREMENTS

5.1 Ethical and regulatory review

Necessary approvals of the Clinical Investigational Plan (CIP), the subject Information sheet and Informed Consent Form (ICF) must be obtained before enrolment of any subject into the investigation. The written approvals, including an identification of the investigation and the date of review, will be filed in the Sponsor File and at the Investigation Site File.

It is the responsibility of the Sponsor to keep the IEC and Competent Authority informed of Serious Adverse Events (SAEs) or device deficiencies that could have led to a SAE, any substantial amendments to the CIP and any safety updates/reports during the investigational period, according to local requirements.

All correspondence with the IEC and Competent Authority will be filed both in the Sponsor Trial Master File (TMF).

5.2 Ethical conduct of the investigation

The investigation will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects that were adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions and ISO 14155:2020.

The Declaration of Helsinki is included as Appendix 13.2 to the CIP.

5.3 Subject information and consent

It is the responsibility of the Investigator to give each potential investigational subject, adequate verbal and written information regarding the objectives and the procedures of the investigation as well as any risks or inconvenience involved before including the subject. The subject must be informed about the right to withdraw from the investigation at any time. The subject should be allowed sufficient time for consideration of the proposal.

Furthermore, it is the responsibility of the Investigator to obtain signed informed consent from all subjects before including them in the investigation. The ICF must be signed and personally dated by

the subject and by the Investigator before any investigation-specific procedures are performed, including screening procedures. A copy of the Subject Information and the signed ICF will be provided to the subject.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the Case Report Form (CRF). The signed Subject Information sheet and ICF should be filed by the Investigator for possible future audits and/or inspections.

The final version of the Subject Information sheet and ICF are submitted to the IEC and concerned Competent Authority and must not be changed without permission from Sponsor, the Competent Authority and the local IEC.

The subjects will be asked for participation in the clinical investigation when seeking care for suspicious cutaneous lesions at the primary care centre. The subject can also be identified if an investigator sees a suspicious lesion when examining the subject for another purpose. If the subject's lesion(s) is suspected of MM or MM cannot be ruled out the subject is asked to participate in the investigation. The subject receives oral and written study information and will have time to read the information and ask any questions. If the subject voluntarily agrees to participate the consent form is signed before any investigation assessments are collected.

5.4 Subject data protection

The ICF includes information that data generated during the investigation will be recorded, collected and processed and may be transferred to countries within the European Economic Area (EEA). In accordance with the General Data Protection Regulation 2016/679 (GDPR), the data will not identify any persons taking part in the investigation.

The potential investigational subject should be informed that by signing the ICF he/she approves that authorized representatives from the Sponsor and sponsor representatives (i.e CRO), the IEC and the Competent Authorities, as applicable, have direct access to his/her medical records for verification of clinical investigational procedures.

To ensure the confidentiality of the subjects in the clinical investigation each subject will receive a pseudonymised subject ID within the database. The subject identification list will be kept separately by the site in a secure manner. The Investigator must file a subject identification list, which includes sufficient information to link records, i.e. the CRF and clinical records. This list should be preserved for possible future inspections/audits but should not be made available to the Sponsor or sponsor representatives except for monitoring or auditing purposes.

All data going to and from Trial Online are secured using strong encryption. It is not possible to gain access to data being transmitted from the web browser. The databases comprising the system are located in a secure data centre with strong physical protection in place. Access to the servers is protected by using strong authentication (individual username and password combination as well as a one-time password). Data is backed up every 24 hours and all backup data is backed-up once every 24 hours to a separate data centre facility. Access to infrastructure elements and backup copies is limited and controlled. User access will be checked and followed up on a regular basis during the investigation.

5.5 Risks and benefits of the Investigational Medical Device and clinical investigation

5.5.1 Risks/benefit associated with participation in the clinical investigation

There are no foreseen risks to participate in the clinical investigation than those according to current standard of care for the target population. The IMD is a software and not in contact with or used by the subjects. The subjects will receive the same standard of care as they would if they were not participating in the clinical investigation. The outcome of the IMD AI will not influence the treatment of the subject. The IMD log-in screen is marked “use only for clinical investigation” to ensure it will only be used by investigators participating in the clinical investigation.

5.5.2 Contraindications

It is not recommended analyzing lesions in the following situations.

- Cutaneous lesions masked by an excessive amount of hair.
- Any form of body modification by injecting ink, dyes, and/or pigments covering or surrounding skin lesions.
- Any form of scarring of tissue due to injury.
- Damaged or injured non-intact skin with lesions.
- Cutaneous lesions on non-human subjects.

5.5.3 Risk-to-benefit rationale

There are no additional risks for participating subjects as they will receive the standard of care as per routine at the investigations site. The only added procedure is an additional photo taken for the evaluation by the AI. The healthcare personnel in the investigation will have to perform additional

documentation and answer if the device may be of benefit if applied as diagnostic support after CE-mark. Thus, there are no or low risks and possible benefits, thus the ratio is favourable.

6 INVESTIGATOR(S) AND INVESTIGATION ADMINISTRATIVE STRUCTURE

This clinical investigation,sponsored by Karolinska Institutet (KI) and Region Östergötland (RÖ) Centre for Primary Care, will be conducted at several primary care centres, see appendix **13.4** . Clinical monitoring and Data Management will be provided by Key2Compliance. Key members of the Sponsor, and Key2Compliance project teams and sub-contractors are presented below.

Sponsor	**Principal Investigator & Sponsor's Signatory** Magnus Falk Phone: +46 (0)70 810 61 76 E-mail: magnus.falk@liu.se **Sponsor Medical Officer** Panos Papachristou Phone: +46 (0)70 229 88 92 E-mail: panos.papachristou@ki.se
Investigational site(s)	Magnus Falk and Panos Papachristou are the Principal Investigators (PIs) for all 30 sites in the clinical investigation. Magnus Falk is, in addition, the NCI. They are responsible PIs for Primary Care centres in their and adjacent regions. For site list see **Appendix 13.4.** A detailed description is listed in the

document 07e_Site structure, GCP Resources and PI oversight_2.0_ddJan2022. Magnus Falk and Panos Papachristou will delegate responsibilities to sub-investigator at each of the 30 sites.

CRO – Data Management and Clinical Monitoring

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Signatures required are provided in Appendix 13.1.

7 INTRODUCTION

Dermalyzer is an Artificial Intelligence (AI) application (app) that allows medical professionals to take pictures of cutaneous lesions with the help of a smartphone camera. A dermatoscope is connected to the smartphone camera and is used to take the digital image of cutaneous lesions with suspicion of melanoma. Based on image processing algorithms, the app does a detailed analysis of the captured cutaneous lesion. Dermalyzer provides information for medical professionals as decision support when assessing skin lesions such as melanoma. The input from the device is not intended to be used as sole information for diagnosis. The software application can be used on either a mobile or a computer.

Dermalyzer is a Medical Device that is not CE-market yet, the plan is to collect clinical data in the planned Clinical Investigation. In the clinical investigation, the technically verified and validated MDSW version 0.0.2 dated 2022 will be applied.

The aim of the current clinical investigation is to determine the diagnostic accuracy of the Dermalyzer device. This medical device investigation has been initiated by the investigators, thus the Sponsor and Investigator is the same under these circumstances.

7.1 Background

Malignant melanoma is a type of tumor resulting from an uncontrolled proliferation of melanocytes (pigment-producing cells), a type of cell found in the mucous membranes, eyes, and innermost layers of tissue covering the brain and spinal cord[1,2]. Despite advances in both diagnosis and treatment of malignant melanoma, the disease is still a major challenge within healthcare[1]. The incidence of the disease among several fair-skinned populations has increased with as much as 4-6 percent yearly[1,3] and melanoma is one of the cancer types with the highest average years of life lost per death (15 years), so-called AYLL[4]. Melanoma accounts for only 5 percent of cutaneous malignancies, but can be attributed to most skin cancer deaths[1].

During 2020 it was estimated that Europe had a total incidence of approximately 150,000 and the total number of deaths caused by melanoma was approximately 26,000. North America had a total incidence of approximately 105,000 and the total number of deaths caused by melanoma was approximately 8,500. Oceania had a total incidence of approximately 19,000 and the total number of deaths caused by melanoma was approximately 2000[5].

Primary care and general practitioners play a vital role in detecting patients with suspected skin lesions and thus in detecting melanoma at early stages[6]. Histopathology (or 'Pathologic anatomic diagnosis', PAD) is considered the gold standard in melanoma diagnosis. For histopathological diagnosis the suspected lesion is excised and inspected by a dermatopathologist, who can report on characteristics, such as melanoma subtype, tumor thickness and ulceration. If the malignancy is not detected at an early stage and is allowed to metastasize and spread outside its primary location, it is more challenging to treat and the chance of survival decreases[1]. If detected at an early stage, excision of the skin lesion is associated with a high chance of survival[7]. On the other hand, unnecessary excision of benign skin lesions are common and leads to increased morbidity as well as increased healthcare costs[8]. The direct and indirect healthcare and societal costs for diagnosing and treating malignant melanoma, as well as costs associated to melanoma deaths, are significant [1,8].

Detection and treatment of melanoma in early stages takes up only a fraction of the resources needed to treat melanoma in later stages. Early detection can thus contribute to cost savings[7]. Innovative technological solutions used in secondary preventive strategies have the potential to reduce costs[1,7]. Although significant progress has been made in recent years, much more research and innovation are needed[3]. Given the severity of the disease, in terms of rising incidence and mortality rates and the associated costs, it is important to develop cost-effective methods to facilitate skin lesion examinations. Diagnosis of melanoma in early stages is in the best interest to patients, payers and the healthcare system[7].

Artificial intelligence (AI) has, in controlled experimental environments, shown promising results in diagnosing malignant melanoma[9]. Areas such as medical image analysis have almost completely shifted digital images[10]. In turn, and in conjunction with AI, enabling physicians to perform faster and more accurate image interpretation[11].

Technological advances have also made it possible to implement AI, with significant potential for improving healthcare systems and processes[12,13]. These technological advances have enabled opportunities for improving healthcare instruments such as diagnostic decision support systems (DDSS)[14]. Through decision support systems, AI can partially alleviate and overcome digitalization challenges in healthcare.

7.2 Investigational Medical Device

The Investigational Medical Device (IMD) is Dermalyzer,an Artificial Intelligence (AI) application (app) that allows medical professionals to take pictures of cutaneous lesions with the help of a smartphone camera. A dermatoscope is connected to the smartphone camera and is used to take

the digital image of cutaneous lesions with suspicion of melanoma. Based on image processing algorithms, the app does a detailed analysis of the captured cutaneous lesion. Dermalyzer provides information for medical professionals as decision support when assessing cutaneous lesions such as melanoma. The input from the device is not intended to be used as sole information for diagnosis. The medical software (MDSW) application can be used on either a mobile or a computer.

A more detailed description is given in Section 9.4

7.3 Clinical experience

The AI has been trained by batches of photos collected during clinical use of dermoscopes. Several experienced clinicians have been part of the device development. This is the first time the device is tested in clinical settings.

7.4 Rationale for the investigation

There is a clear benefit at group level if the methodology can contribute to safer, more accurate and efficient diagnostic procedures of patients seeking primary care for skin lesions of concern, while there are, on the other hand, no significant risks associated with the study. Potentially fewer cases of unnecessarily excised benign skin lesions would contribute to improved access to care for those with malignant lesions, thereby also increasing the prerequisites for early cancer detection. Overall, the benefits of the study are clearly considered to outweigh the risk(s).

8 INVESTIGATIONAL OBJECTIVES AND ENDPOINTS

8.1 Primary objective

The primary objective of the investigation is to determine the diagnostic precision of the device; to answer at which level the AI tool Dermalyzer can identify malignant melanomas among cutaneous lesions that are assessed in clinical use due to any degree of malignancy suspicion.

8.1.1 Primary endpoint

The primary endpoint will be measured as the true proportion; by testing if the device based on artificial intelligence (AI) gives correct results as compared with the result of the lesion analysis (the final classification by PAD) in at least a certain proportion (π) of the analyses.

8.2 Secondary objectives

As secondary objectives a number of analyses will be done.

To evaluate usability and applicability in clinical praxis of Dermalytics by users (medical professionals).

To gain an increased knowledge and understanding of how digital tools enhanced co-artificial intelligence can assist physicians with the right support for an earlier diagnosis of malignant melanoma.

8.2.1 Secondary endpoints

User questions including System Usability Scale to evaluate the usability and applicability in clinical praxis.

8.3 Exploratory objectives

To explore health economic aspects of improved diagnosis support.

8.3.1 Exploratory endpoints

Collecting health economic related information by survey to participating sites.

9 INVESTIGATIONAL PLAN

9.1 Overall investigational design and schedule of events

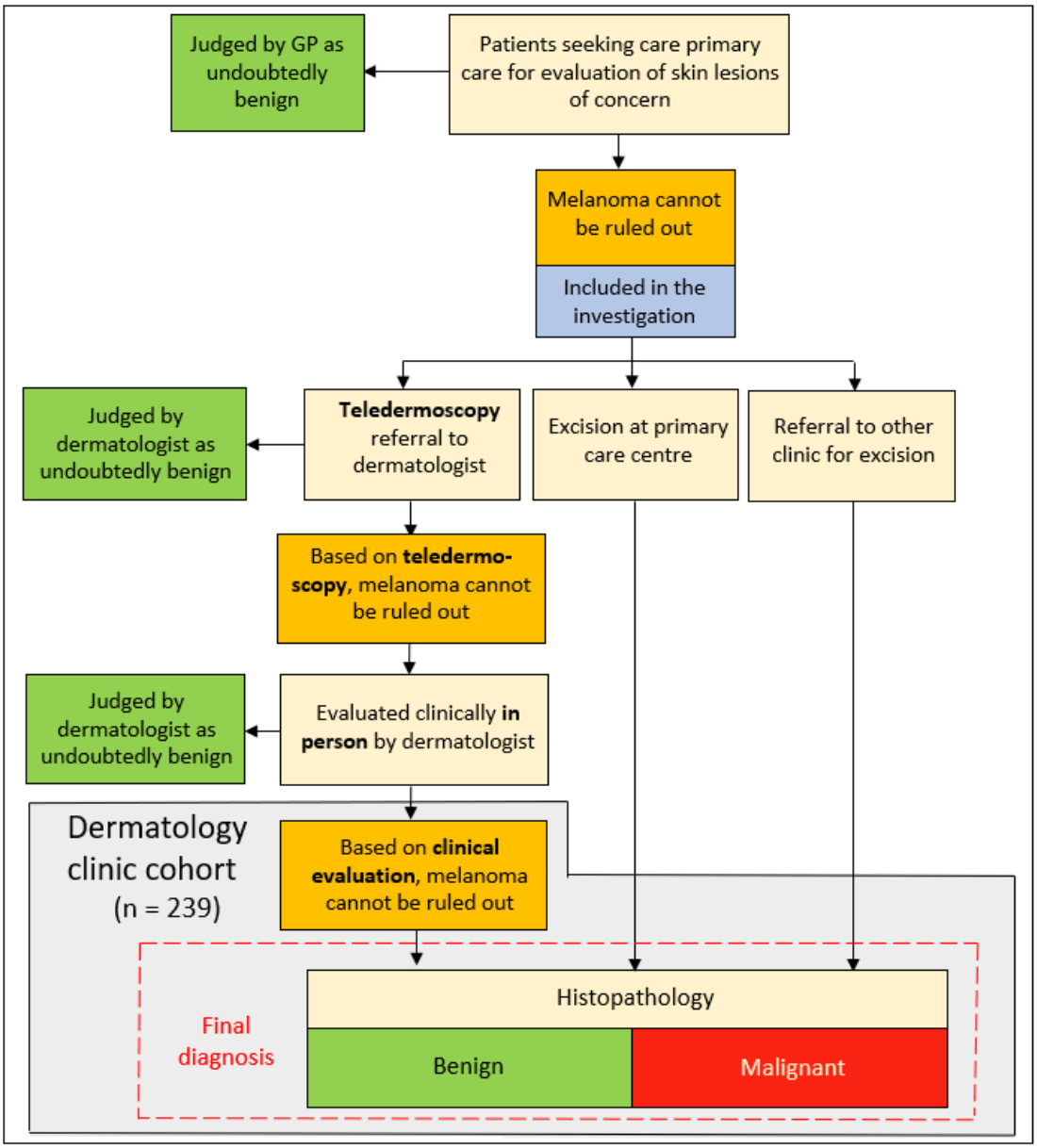
The subjects will be included from primary care centres. If the subject’s lesion(s) is suspected of melanoma or melanoma cannot be ruled out the subject is asked to participate in the investigation. The investigator examines the subject's lesion(s) (with or without a dermatoscope) and may also take dermoscopy images according to standard of care. The investigator then makes his clinical

assessment of the subject lesion(s) based on established clinical decision algorithms (such as "Chaos and clues", "3- or 7-point checklist", or the ABCDE criteria) of whether there is a suspicion of melanoma, according to the usual clinical routine (also includes very low suspicion that cannot be completely dismissed). The investigator decides on action based on his or her MM suspicion (excision at the primary care centre or referral for excision or referral to a dermatologist for further assessment), see figure 1.

If the subject has agreed to participate in the investigation, the investigator indicates in the eCRF his clinical suspicion level of MM and decided action.

The investigator takes images of the lesion(s) again, this time with a mobile phone, containing the IMD AI SW, connected to a dermatoscope, and follows the on-screen instructions, see appendix 13.3. The image is processed by the AI SW and the results are visible on the screen within seconds. A unique auto generated code number is also presented. The code number is registered on the enrollment log and in the eCRF. The investigator records how he considers that the degree of suspicion of MM (higher vs lower) would have been affected by the AI SW result if it had been the governing body for the treatment. When the PAD result is available the outcome is documented in the eCRF.

Figure 1. Investigator workflow for assessing MM suspicion and action to be taken



Visits and assessments will be performed as described in Table 9.1. Each assessment is further described in Section 9.5.

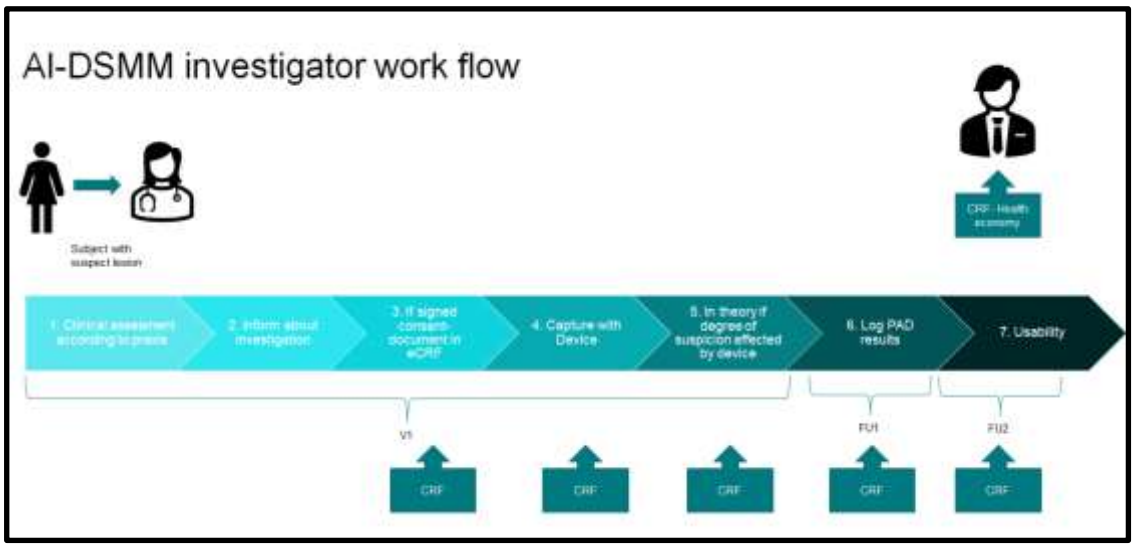
Table 9.1 Schedule of events

	Baseline/ Visit 1	Follow-up 1	Follow-up 2
	Day 1	Day 30(+/-30)	After at least 10 subjects
Informed consent + photo consent	x		
Inclusion/Exclusion criteria	x		
Demographics (Age, melanoma history/family history, race)	x		
Fitzpatrick skin type (exclude V-VI	x		
Lesion assessment (body area, number of lesions, size)	x		
Clinical assessment (naked-eye examination, with or without dermoscopy,) “Chaos&clues”, 3-point checklist, ABCDE criteria	x		
AI photo	x		
Histopathology (PAD)		x	
In theory if degree of suspicion affected by device	x		
User questionnaire			x[1]
Health economic outcomes			x[2]
Adverse Event	x	x (from journal if relevant)	

[1]To be answered by Investigators at one occasion only

[2]To be collected by each region's actual cost for PAD and excision or data collected via the KPP-database.

Figure 2. Overview of workflow



9.2 Justification for the design of the clinical investigation

The device has reached the development stage where a verification of its applicability in the clinical settings is warranted. The design of the investigation is that of a safe way to test the device in clinical use without changing the standard- of-care for the participating subjects, while collecting data on possible benefits of the use of the device.

9.3 Selection of investigational population

9.3.1 Recruitment

Subjects having lesions where MM cannot be ruled out will be identified for inclusion in this CI. The subject visits the primary care clinic for examination of one or more skin lesions of concern, or the investigator detects a suspected skin lesion in connection with another cause of visitation.

9.3.2 Number of subjects

To reach the target of 239 eligible lesions with a PAD approximately 500 lesions will need to be included, that is up to 500 subjects. The CI needs to be able to analyse 239 PAD verified lesions where at least 12 lesions need to be PAD positive responses (confirmed MM). In case, after 500 subjects/lesions have been evaluated and the 12 positive PAD have not been obtained, further subject enrolment will continue until 12 positive PAD have been reached.

9.3.3 Screening and enrolment log

Each clinic will keep a log of all subjects screened and included. The reason for screening failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects included but not completed.

9.3.4 Inclusion criteria

For inclusion in the investigation, subjects must fulfil all the following criteria:

1. *Patients ≥18 years*
2. Patients attending a healthcare facility with at least 1 suspicious skin lesion where MM cannot be ruled out.
3. *Willingness and ability to provide informed consent.*

9.3.5 Exclusion criteria

Subjects must not enter the investigation if any of the following exclusion criteria are fulfilled:

1. *Cutaneous lesions that are considered as benign by the investigator and thus not subject for further clinical investigation*
2. *Cutaneous lesions in areas that are not suitable for dermoscopic imaging*
3. *Cutaneous lesions in areas with any form of scarring of tissue due to injury*
4. *Damaged or injured non intact skin where the cutaneous lesion is located*
5. *Individuals with skin type V and VI according to the Fitzpatrick scale (darker brown or black coloured skin)*

6. *Cutaneous lesions in areas covered by tattoos*
7. *Cutaneous lesions in abundantly hairy skin areas (provided the area cannot be shaved freely from the hair to allow clear view for the dermatoscope)*
8. *Images where the entire lesion is not inside the photo*
9. *Images that are out of focus*

9.3.6 Criteria and procedures for subject withdrawal

An investigational subject should be withdrawn from the intervention if, in the opinion of the Investigator, it is medically necessary, or if it is the expressed wish of the subject. In this CI the subjects only participate a short time at one visit however a subject can always at any time withdraw consent.

9.4 Investigational Medical Device description

9.4.1 General description

Dermalyzer is an image analysing software application functioning as decision support to healthcare professionals on assessing suspected cutaneous lesions for skin cancer. The device should be used in combination with a medical professional assessment of the suspected lesion. The software application uses a mobile camera to capture images of cutaneous lesions.

9.4.2 Intended use

The device is intended to be used as a decision support system for assessing cutaneous lesions suspected of being melanomas. The input from the device is not intended to be used as the sole source of information for diagnosis. The device should be used in combination with a medical professional assessment of the suspected lesion. The service does not provide any other diagnostic use.

9.4.3 IMD classification

Non CE marked Medical Device Software (MDSW) class IIb.

9.4.4 Manufacturer details

AI Medical Technology AIM AB

Sturegatan 44 D

114 36 Stockholm

9.4.5 Summary description of the IMD

An overview picture of the IMD is given in Figure 3.

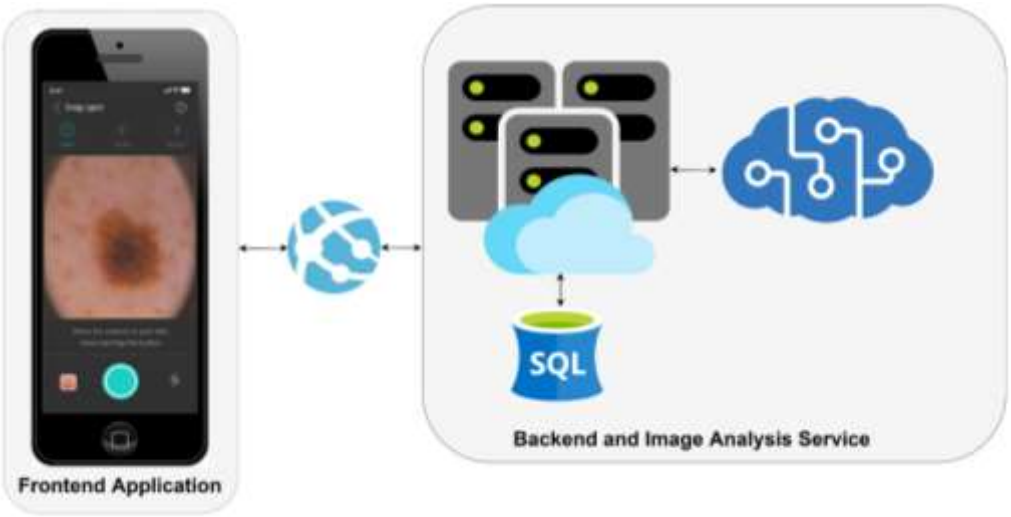


Figure 3 - Overview of the Investigational Medical Device - Dermalyzer Clinical Decision Support System

9.4.6 Intervention procedure

Dermalyzer shall be used by medical professionals in primary care settings. The software shall be used as a decision support system to assess cutaneous lesions on patients aged 18 or more having suspicious melanoma lesions.

Detailed Instructions for use (IFU) are included in Appendix 13.3.

9.4.7 Packaging, labelling and storage of the Investigational Medical Device

For the clinical investigation, the application Dermalyzer from Google Play or App Store is already downloaded on a compatible Android or iOS mobile device. Operating system compatibility for iOS is 13.0 and later and Android is Pie 9 (API Level 28) and later. Dermatoscopic adaptors will be used connected to the phone. The sites can have different types of smartphones and versions will be captured in the eCRF. The application Dermalyzer log-in screen is marked “Use only for Clinical Investigation”, see Figure 4.

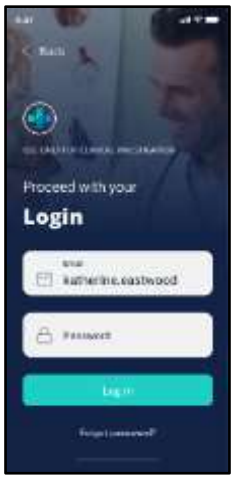


Figure 4. Dermalyzer Log-in Screen

9.4.8 Compliance with IMD usage

The IMD must be used according to the IFU, see Appendix 13.3.

9.4.9 Accountability/traceability of the Investigational Medical Device

The accountability of the IMD will be documented both which mobile phones that will be provided to which site but also which version of the device that is applied. The sponsor-investigator or delegated personnel is responsible to ensure traceability. Each site will be provided with a phone

with a unique sim-card and each phone will have a unique IMEI number. The phones sent to each site will be controlled and locked to only allow certain functions, which means that full control, over all software installed on the phones in general and which version of the software that is installed on each device in particular, can be achieved. The dermatoscope model that will be used as attachments to the phones during the investigation is the DermLite D3 and Heine iC1/7.

9.4.10 Blinding

The Investigators will have to document their assessment of the included lesion(s) in the eCRF before taking the IMD image in order not to be influenced by the IMD result. When the outcome of the IMD AI result is available the Investigator will evaluate if his/her decision would have changed if taking the result of the AI into consideration.

9.5 Investigational assessments

The investigational assessments are described in the sections below and the timing of these assessments is detailed in the schedule of events (Table 9.1, Section 9.1).

9.5.1 Demographics and other baseline characteristics

9.5.1.1 Informed consent

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 5.3.

9.5.1.2 Demographic information

The following demographic data will be recorded: age, gender, Fitzpatrick skin type (I-IV), ethnic origin.

9.5.1.3 Medical history

Medical history relevant for the investigation, as judged by the Investigator, will be obtained, as skin cancer history.

9.5.2 Clinical performance assessments

9.5.2.1 Assessment 1

Dermoscopy image with mobile phone and attached dermatoscope

9.5.2.2 Assessment 2

The method applied according to standard of care at each site (Chaos & clues", "3- or 7-point checklist", ABCDE concept or other) for the investigator to make his/hers clinical assessment of the subjects lesions to establish whether there is a suspension of MM will be documented in the CRF.

9.5.3 Laboratory assessments

Histopathology results (PAD) from excised lesions according to standard routine.

9.5.4 Clinical safety assessments

9.5.4.1 Assessment 1

All considered reportable events in accordance with MDR, will be captured. See section below for the Serious Adverse Event (SAE) and Device Deficiency (DD).

9.5.5 Health economic assessments

9.5.5.1 Assessment 1

A survey will be collecting health economic related information to participating sites

9.5.6 Safety reporting, Adverse Events and Device Deficiencies

The reporting modality for the current clinical investigation is “Pre-market clinical investigations covered by Articles 62 and 74(2) of the MDR conducted with:Non-CE marked device”.

Adverse Event (AE) and Serious Adverse Event (SAE)

- **AE -** Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device
- **SAE-** Any adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, that resulted in any of the following:

   i. life-threatening illness or injury,

   ii. permanent impairment of a body structure or a body function,

   iii. hospitalisation or prolongation of patient hospitalisation,

   iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

   v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Device Deficiency (DD)
Is defined as any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.
Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Considered reportable events in accordance with MDR

- any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
- any device deficiency that might have led to SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
- any new findings in relation to any event referred to in points a) and b)

Reporting requirements
Reportable events will be reported by the KI/RÖ or AIMT (sponsor-investigator) of the clinical investigation.

Reporting timelines

a) All reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it - **Immediately, but not later than 2 calendar days after sponsor-investigator are made aware of the new event**
b) Any other reportable events or a new finding/update to it - **not later than 7 calendar days after sponsor-investigator are made aware of the new event**

In the event of a reportable event, it should be documented in the subject's medical record, documented in the eCRF as well completion of the Clinical Investigation Summary Safety Report Form (appendix 13.5). The Clinical Investigation Summary Safety Report Form needs to be filled in/updated for each reportable event or for new findings/updates to already reported events.
For the investigational site and during the clinical investigation, the investigator needs to report the reportable event to the sponsor immediately, but not later than 3 calendar days after investigation site study personnel's awareness of the event.

Causality assessment

The relationship between the use of the medical device and the occurrence of each adverse event shall be assessed and categorized. Each SAE will be classified according to four different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

Only causality level 1 (i.e. "not related") is excluded from reporting. If higher causality level than "not related", the event should be reported. Any device deficiency that might have led to a SAE should be reported.

Reporting form (Appendix 13.5_Clinical Investigation Summary Safety Report Form_1.0_20Jan2022

- Form is study specific and covers only the given clinical investigation
- The template form contains inserted filters and functionality to facilitate use of preferred terminology in the reporting. These are important for the analysis and should be maintained

- The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported.

9.6 Data quality assurance

This clinical investigation will be conducted in compliance with the CIP, relevant Standard Operating Procedures (SOPs), the principles of the European Standard EN ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice (GCP), MDR (EU) 2017/745 and any other applicable regulatory requirements.

9.6.1 CIP adherence

The Principal Investigator is not allowed to deviate from the CIP.

The Sponsor-investigator is responsible for documenting and analysing any deviations and assessing their significance. Corrective action will be implemented to avoid repeated deviations, which may include suspending the clinical investigation and/or amending the CIP.

9.6.2 Monitoring

The monitoring will be done according to the Monitoring Plan with the purpose to verify that all aspects of the CIP are complied with and that the conduct of the investigation conforms to applicable regulatory requirements and established rules for Helsinki Declaration and GCP/ISO14155, to protect the rights, safety and well-being of the human subjects.

Monitoring will be done as on-site or remote visits and during central monitoring.

During the monitoring visit the monitor will verify the Informed Consent procedure, review CRFs and source data, check SW version for the IMD, reporting of DD, etc. The extent of SDV and the strategy for risk-based monitoring will be described in the Monitoring Plan.

For the purpose of SDV, the Monitor must be given direct access to original clinical records according to the Source Data Agreement.

9.6.3 Audits and inspections

Authorized representatives of Sponsor, or a Competent Authority may perform audits or inspections at the investigational site. The purpose of an audit or inspection is to systematically and

independently examine all investigation-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the CIP, EN ISO 14155 and any other applicable regulatory requirements.

The site Investigators are required to inform the Sponsor-Investigator immediately of an inspection requested by a Competent Authority or IEC.

9.6.4 Case Report Forms

Case Report Forms must be completed and signed by authorized personnel for each included subject.

All data must be entered in English. The CRFs should always reflect the latest observations made during the subject's participating in the investigation. Therefore, the CRFs should be completed as soon as possible during or after the subject's visit.

The Investigator must verify that all data entries in the CRFs are accurate and correct by signing the completed CRF.

The completed CRFs should be made available for checking of completeness and accuracy by the Monitor as agreed in advance.

9.6.5 Source Data

A separate source data document will be generated for the investigational site before start of enrolment, specifying the location of the source of derived information appearing in the CRF. This document must be signed by the Sponsor-Investigator and the Monitor to confirm agreement before the start of recruitment.

The Investigator should guarantee access to source documents to the Monitor, Competent Authorities and the IECs, if required.

9.6.6 Training of investigation staff

In connection to Site initiation visit, all sites will be trained on the ISO 14155 (GCP training) via a video, the sites will have time to ask questions during a Q&A. Before inclusion of the first investigational subject the Monitor/sponsor will perform an Initiation Visit at the investigational site, this may be done remotely, if applicable. The requirements of the CIP and related documents will be reviewed and discussed, and the investigational staff will be trained in any investigation specific procedures and system(s) utilised. A Site Initiation slide deck will be reviewed with the site, to

ensure for example Informed Consent, medical record keeping, and safety reporting and timeline are reviewed in detail with the sites. The training will include IMD usage and mitigation of residual risks.

It is the responsibility of the Principal Investigator to ensure that all personnel involved in the investigation are fully informed of all relevant aspects of the investigation and have detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this investigation must be forwarded to the staff involved in a timely manner. Magnus Falk and Panos Papachristou are the PIs for the investigation and have oversight at the 30 other clinical investigational sites. A more detailed information will be given in the document 07e_Site structure, GCP Resources and PI oversight_1.0_20Jan2022.

The Investigator will keep a list of all personnel involved in the investigation together with their function and investigation related duties delegated. A Curriculum Vitae (CV) will be available for all staff delegated investigation-specific duties.

9.7 Statistical methods and determination of sample size

9.7.1 General

Data from all variables will be presented by means of descriptive statistics and all data will be presented by line listings.

Descriptive statistics implies providing the number of observations, number of missing data, minimum, median, maximum, mean and standard deviation for all continuous and ordered categorical data. Binary data and non-ordered categorical data will be presented by count and percentage in each category.

9.7.2 Demographics and other baseline characteristics

Demographics and other baseline characteristics will be presented using descriptive statistics.

9.7.3 Analysis of clinical performance

9.7.3.1 Primary Objective and *Endpoint*

The primary objective of the investigation is to determine the diagnostic precision of the device; to answer at which level the AI tool Dermalyzer can identify malignant melanomas among cutaneous lesions that are assessed in clinical use due to any degree of malignancy suspicion.

The primary endpoint will be measured as the true proportion; by testing if the device based on artificial intelligence (AI) gives correct results as compared with the result of the lesion analysis (the final classification by PAD) in at least a certain proportion (π) of the analyses.

9.7.3.2 Secondary Objective and *Endpoint*

The primary objectives are to evaluate usability and applicability in clinical praxis of Dermalyzer by users (medical professionals) and to gain an increased knowledge and understanding of how digital tools enhanced co-artificial intelligence can assist physicians with the right support for an earlier diagnosis of malignant melanoma.

The second endpoint will be measured by User questions including System Usability Scale to evaluate the usability and applicability in clinical praxis. In addition to these endpoints, a number of analyses will be done that can be found in the SAP.

9.7.3.3 Exploratory Objective and *Endpoint*

The exploratory objective is to explore health economic aspects of improved diagnosis support.

The exploratory endpoint will be measured by collecting health economic related information by survey to participating sites.

9.7.4 Analysis of safety

9.7.4.1 Endpoint 1

The main risks identified for similar devices are incorrect diagnosis (false positives and false negatives) due to limitations in the training data set that was used to develop the software. According to the risk management, the only unacceptable risk identified for Dermalytics is that some individuals, including patients with ulcerations (damage to the skin) , external modification to the skin, absence of surrounding skin (normal skin around), will be excluded. This is stated in the IFU for

the IMD. The prevalence of incorrect diagnosis will be captured in the primary endpoint analysis, as well as the possibility of reduced risk of missing malignant melanomas (false negatives). The consequences of false negatives will be evaluated by collecting health economic data. To this end, the participating clinicians will be provided a survey with questions on how the use of Dermalytics would affect health economic aspects, such as time to treatment, number of visits to dermatologists and number of excisions.

9.7.5 Analysis data sets

The data will be analysed using three analysis sets:

- Intention To Treat (ITT)
    - All correctly (i.e., fulfill all entry criteria) included subjects are included in this analysis set.
- Per Protocol (PP)
    - This is a subset of the ITT analysis set and all patients that are included in the ITT analysis and as well has followed all major procedures in the investigation (to be defined prior to start of the statistical analysis).
- Safety Analysis Set (SAS)
    - Includes all subjects who have been exposed to the Demlayzer

9.7.6 Determination of sample size

The general practitioner (GP) will only include subjects in the investigation with lesions where melanoma cannot be ruled out. All lesions where melanoma cannot be ruled out will be sent for an analysis (final classification) to confirm – or not confirm – if the suspected melanoma is a melanoma or not. Each lesion where melanoma cannot be ruled out will be analysed by the IMD and the IMD will classify each lesion where melanoma cannot be ruled out as “Low Risk of being a melanoma” (Low) or “High risk of being a melanoma” (High).

In Table 1 the possible outcomes are described and (A+D)/(A+B+C+D) is the proportion of correct classifications by the IMD.

Table 1 Outcome (m = number of patients) for a binary variable where two groups of observations are linked together.

		The AI device		
		High	Low	Total
Final classification	Melanoma	A	B	A+B
	Not melanoma	C	D	C+D
	Total	A+C	B+D	A+B+C+D

The expected value of (A+D)/(A+B+C+D) is denoted π and then the hypotheses of interest are

$$H_0: \pi \leq \pi_0$$

$$H_1: \pi > \pi_0$$

The null-hypothesis (H_0) will be rejected if the one-sided p-value is less than a. If $\pi = \pi_1$ the power to reject H_0 should be β.

Typically, a = 2.5 % and β = 80 % or 90 %. The p-value will be calculated using the exact Binomial test.

In a successful investigation H_0 is rejected and then H_1 is accepted.

In Table 2 the needed number of lesions is presented based on the formula above and for statistical power 90%.

Table 2 Number of lesions where melanoma cannot be ruled out needed to achieve **80%** power to reject (i.e. get a one-sided p-value less than 2.5%) the null-hypothesis by proportions to be rejected (i.e., π_0) and by assumed true proportions (i.e. π_1). Calculated by Sample Size a single proportion V01.xls.

True Proportion (π_1)	Proportion to be rejected (π_0)					
	50%	60%	70%	80%	90%	95%
55%	783	.	.	.	.	.
60%	194	.	.	.	.	.
65%	85	742	.	.	.	.
70%	47	182	.	.	.	.
75%	29	78	638	.	.	.
80%	20	43	153	.	.	.
85%	14	26	64	471	.	.
90%	10	17	34	108	.	.
95%	7	11	19	42	239	.

100%	4	6	9	16	35	73

The set expectation of 95% true proportion is based on in-silico experiments on a proprietary dataset of images which found a sensitivity of 95.1 ∓0.6%.

The accuracy of AI decision support will be measured against gold standard (PAD) as well as against experienced dermatologists and general practitioners (average) and verified at: sensitivity> 95%, specificity> 75%, numbers needed to excise (NNE) <7, positive predictive value (PPV))> 15% and negative predictive value (NPV)> 99.5%. The average sensitivity for general practitioners in previous meta-analyzes is estimated at about 81%.

9.8 Data Management

The Principal Investigator or other qualified and delegated personnel will report data through Trial Online, a web based electronic Data Capture (EDC) system that manages electronic Case Report Forms (eCRFs). Trial Online is fully compliant with FDA 21 CFR Part 11, ISO-14155 and GDPR.

The Data Manager will write a Data Management Plan (DMP) outlining the data management activities in this investigation. The Sponsor will review and approve the DMP.

Each site personnel will receive a unique login to access the system. Site personnel will be trained before receiving access. All data must be entered in English. Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. The CRFs should always reflect the latest observations made during the subject's participation in the investigation. Therefore, the CRFs should be completed as soon as possible during or after the subject's visit. All data entries and changes done in the eCRF are captured in an audit trail.

The Principal Investigator must verify that all data entries in the CRFs are accurate and correct by signing the completed CRF. Assessments that are not done or not applicable should be stated in the eCRF. The Data Manager and/or Monitor will check the quality of the data and query the data in the eCRF when needed. Pages cannot be signed before all queries are resolved.

Each subject will receive a pseudonymised subject ID within the database. The code key will be kept separately by the site in a secure manner.

The electronic data retention period is of at least 10 years. Archiving of data is performed according to industry standards such as in PDF format.

10 EMERGENCY PROCEDURES

The Principal Investigator is responsible for ensuring that procedures and expertise are available at the investigational site to handle medical emergencies during the investigation.

For this investigation there are no foreseeable emergency situations since the IMD is a MDSW not in contact with the subjects or users.

11 MANAGEMENT OF THE INVESTIGATION

11.1 CIP Amendments

Any proposed change to the approved Final CIP (including appendices) will be documented in a written and numbered CIP amendment. All amendments including substantial changes to the CIP or to the Subject Information/ICF must be submitted to the appropriate IEC and Competent Authority for approval, according to applicable national regulations.

11.2 Time table

The end of the clinical part of the investigation is defined as the enrolment of approximately 500 lesions where MM could not be ruled out, to reach the target of 239 evaluable (having PAD outcome result) lesions, with 12 positive PAD results. It is estimated that the PAD results will come from the laboratory within approximately 2 months time frame from each excision.

The enrolment period of the investigation is expected to start in Quarter 1, 2022 and to be completed by Quarter 3, 2022.

11.3 Discontinuation of the investigation

The Sponsor reserves the right to discontinue the investigation at any time, but intends only to exercise this right for significant and documented reasons (e.g. valid scientific or administrative reasons, risk to the subjects or non-compliance by the Investigator).

After such a decision all CRFs should be completed as far as possible.

The Sponsor must inform the Competent Authority and IEC concerned as appropriate about any premature termination.

11.4 Reporting and publication of investigation results

A Clinical Investigation Report, in compliance with ISO 14155, Annex D, describing the conduct of the investigation, the statistical analysis performed and the results obtained, will be prepared by RÖ/KI.

A summarizing report will be submitted to the Competent Authorities within 12 months from end of investigation (last histopathology result received and entered in eCRF) or be available on request, as per local requirements.

If the duration of the investigation exceeds one year, the Sponsor must submit an annual safety report to the Competent Authority and to the IEC, if applicable. The report will summarize any SAEs and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical investigation.

The aim is to prepare a scientific publication to describe the results from the clinical investigation, based on the report results.

11.5 Disclosure and confidentiality

All unpublished information concerning the IMD and research carried out by the Sponsor, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and the sole property of the Sponsor/AIMT. Disclosure to third parties must be limited to those undertaking legitimate peer review of the scientific and ethical aspects of the investigation and to those participating, including the recipients of IMD, so that customary medical care and informed consent can be achieved.

- The clinical investigation will be registered in a publicly accessible database e.i clinicaltrials.gov.
- The results of the clinical investigation will be made publicly available.

11.6 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in EN ISO 14155, Annex E) for 10 years after finalization of the Clinical Investigation Report. This includes any original source documents related to the investigation, the Subject Identification List (providing the sole link between named subject source records and anonymous CRF data), the original signed ICFs and detailed records of disposition of IMD.

It is the responsibility of the Sponsor to inform the Principal Investigator/institution as to when these documents no longer need to be retained.

The Sponsor will archive the Sponsor File in accordance with EN ISO 14155, Annex E, and applicable regulatory requirements.

11.7 Insurance/indemnity

Subjects will be covered under Sponsor liability insurance policy through “Patientskadeförsäkringen” or comparable insurance if any private clinic participates as an investigational site. The participating subjects are protected in accordance with national regulations, as applicable.

11.8 Agreements

The sites included in the clinical investigation will not receive any payment from the sponsor to participate in the clinical investigation. The sites have agreed to perform the clinical investigation pro bono. Per each site, the Investigator must comply with all the terms, conditions, and obligations of the Clinical Investigation Agreement and Data Protection Agreement for this investigation. The Clinical Investigator Agreement will be signed by the operations manager at each site, that has also signed the CDA, to ensure that each site has sufficient resources available. Each site has confirmed their ability to participate in the clinical investigation.

Agreements between Sponsor and the investigational site must be in place before any investigation-related procedures can take place, or subjects be enrolled.

12 REFERENCES

1. Matthews, N. H., Li, W.-Q., Qureshi, A. A., Weinstock, M. A. & Cho, E. Epidemiology of Melanoma. in *Cutaneous Melanoma: Etiology and Therapy* (eds. Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia,PA, USA, Ward, W. H., Farma, J. M., & Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia,PA, USA) 3–22 (Codon Publications, 2017). doi:10.15586/codon.cutaneousmelanoma.2017.ch1.
2. Tsatmali, M., Ancans, J. & Thody, A. J. Melanocyte Function and Its Control by Melanocortin Peptides. *J Histochem Cytochem.* **50**, 125–133 (2002).
3. Ward, W. H. & Farma, J. M. *Cutaneous melanoma: etiology and therapy*. (2017).
4. Burnet, N. G., Jefferies, S. J., Benson, R. J., Hunt, D. P. & Treasure, F. P. Years of life lost (YLL) from cancer is an important measure of population burden — and should be considered when allocating research funds. *Br J Cancer* **92**, 241–245 (2005).
5. Global Cancer Observatory. https://gco.iarc.fr/.
6. Jones, O. T., Ranmuthu, C. K. I., Hall, P. N., Funston, G. & Walter, F. M. Recognising Skin Cancer in Primary Care. *Adv Ther* **37**, 603–616 (2020).
7. Voss, R., Woods, T., Cromwell, K., Cormier, J. & Nelson, K. Improving outcomes in patients with melanoma: strategies to ensure an early diagnosis. *PROM* 229 (2015) doi:10.2147/PROM.S69351.
8. Argenziano, G. *et al.* Accuracy in melanoma detection: A 10-year multicenter survey. *Journal of the American Academy of Dermatology* **67**, 54-59.e1 (2012).
9. Ekström, C. & Helenason, J. AI-based malignant melanoma diagnostic decision support system for general practitioners Feasibility study with convergent mixed methods research. (Stockholm University, 2021).
10. Menvielle, L., Audrain-Pontevia, A.-F. & Menvielle, W. *The Digitization of Healthcare*. (2017).
11. Topol, E. J. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* **25**, 44–56 (2019).
12. Dwivedi, Y. K. *et al.* Artificial Intelligence (AI): Multidisciplinary perspectives on emerging challenges, opportunities, and agenda for research, practice and policy. *International Journal of Information Management* **57**, 101994 (2021).
13. Wiljer, D. & Hakim, Z. Developing an Artificial Intelligence–Enabled Health Care Practice: Rewiring Health Care Professions for Better Care. *Journal of Medical Imaging and Radiation Sciences* **50**, S8–S14 (2019).

14. Shinners, L., Aggar, C., Grace, S. & Smith, S. Exploring healthcare professionals' understanding and experiences of artificial intelligence technology use in the delivery of healthcare: An integrative review. *Health Informatics J* **26**, 1225–1236 (2020).

13 APPENDICES

13.1 Signature pages

"I agree to the terms of this Clinical Investigation Plan (CIP)."

Sponsor signatory

Magnus Falk, MD, assoc.professor	*Signature*	*Date*

Sponsor Medical Officer

Panos Papachristou , MD, PhD,	*Signature*	*Date*

Manufacture signatory

Christoffer Ekström, CEO	*Signature*	*Date*

13.1 Signature pages

Coordinating/Principal Investigator(s)

"I agree to the terms of this Clinical Investigation Plan (CIP). I will conduct the investigation in accordance with the procedures specified in the CIP, the ethical principles in the latest version of the Declaration of Helsinki, ICH Good Clinical Practice, ISO 14155 any other applicable regulatory requirements".

Magnus Falk, MD, assoc.professor	*Signature*	*Date*

13.2 Declaration of Helsinki

http://www.up.ac.za/media/shared/Legacy/sitefiles/file/45/2875/declarationofhelsinki_fortaleza_brazil2013.pdf

13.3 Instructions for use

13.4 List of participating sites

13.5 Clinical Investigation Summary Safety Report Form_1.0_20Jan2022