

# BMJ Open Impact of UV-irradiation on electrical impedance spectroscopy of benign nevi: study protocol for a prospective, controlled, clinical study

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## ABSTRACT

**Introduction** The clinical and histological changes of nevi after ultraviolet (UV) irradiation have been studied in detail. In contrast, the impact of UV irradiation on electrical impedance spectroscopy scores of nevi has not been investigated. However, for physicians, it is essential to know the extent to which changes in electrical impedance spectroscopy scores of nevi may be attributed to seasonal effects of UV irradiation.

**Methods** This is a prospective, controlled, clinical study evaluating the impact of UV irradiation on the electrical impedance spectroscopy scores of benign nevi in 50 patients undergoing phototherapy. To this end, benign nevi of patients with a medical indication for phototherapy will be measured by electrical impedance spectroscopy before, during and after UV irradiation. At the same time, non-irradiated nevi of the same patient will be measured to account for changes over time that are independent of direct UV irradiation.

**Ethics and dissemination** Ethical approval was obtained from the ethics committee of the medical faculty of the University of Heidelberg (ethics approval number S-279/2017). The design and the final results of the study will be published and made available to the public.

**Trial registration number** DRKS00012456; Pre-results.

## INTRODUCTION

Several innovative diagnostic tools have been developed to facilitate the differentiation of benign nevi from early melanomas. Melanoma thickness is an important prognostic factor and, therefore, the early detection of melanoma is fundamental for patients' survival.<sup>1</sup> Electrical impedance spectroscopy (EIS) is a non-invasive diagnostic technique for evaluation of tissue structures by applying alternating electrical current and measuring tissue impedance.<sup>1 2</sup> This method is based on differences in electrical impedance between benign,

well-organised and malignant, chaotic tissues. The in vivo electrical impedance of a tissue sample is shaped by tissue properties

## Strengths and limitations of this study

- For the first time, the impact of ultraviolet irradiation on the electrical impedance spectroscopy scores of benign nevi will be evaluated in a prospective clinical study.
- The primary and secondary objectives of this study address open questions of major importance for a correct interpretation of changes in electrical impedance spectroscopy of melanocytic lesions over time.
- This is a non-commercial study, thus ruling out any potential influence of commercial interests or bias.
- Possible limitations of this study lie in its design as a pilot, single-centre study with a small targeted sample size of 50 evaluable participants.

such as the formation of the intracellular and extracellular environment, cell shape and size and cell membrane structure.<sup>2</sup> EIS devices licensed for the US and European markets provide physicians with an output score on a visual analogue scale from 1 to 10. A score of at least four points indicates a positive predictive value of melanoma of >9% and should therefore trigger an excisional biopsy.<sup>2</sup> Melanocytic nevi exposed to ultraviolet (UV) light show clinical, dermoscopic, histological and ultrastructural changes. The secretion of pro-opiomelanocortin (POMC)-derived peptides including melanocyte-stimulating hormone from exposed skin cells enhances the proliferative activity of melanocytes and results in an increase of melanocyte density as well as melanin synthesis.<sup>3 4</sup> To date, there are no studies evaluating the effect of UV irradiation on results of electrical impedance spectroscopy of nevi. However, for clinicians, it is important to know the extent to which changes in EIS scores may be attributed to seasonal effects of UV irradiation.



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## DESIGN/METHODS

### Study design

This is a prospective, controlled, clinical study to evaluate the impact of UV irradiation on the electrical impedance spectroscopy scores of benign nevi in 50 patients undergoing phototherapy.

### Study objectives

The primary objective of this study is to assess the influence of UV irradiation on the EIS scores of nevi by measuring changes in the EIS scores (ranging from 0 to 10) as well as by assessing EIS results as a dichotomous output (EIS score negative (<4)/positive ( $\geq 4$ )). To this end, benign nevi of patients with a medical indication for phototherapy (eg, plaque-type psoriasis) will be measured by EIS before, during and after UV irradiation (intralesional changes over time). At the same time, non-irradiated nevi (protected by a UV-shielding sticker) of the same patient will be measured to account for changes over time that are independent of direct UV irradiation. Changes in EIS scores of irradiated lesions versus non-irradiated lesions of the same patient over time will be compared (interlesional changes over time). Secondary objectives of this study include the assessment of the repeatability of EIS scores by performing two measurements in a row for each lesion at each time point. Repeatability is measurement results under repeatability conditions, where independent measurement results are obtained with the same method on the identical test items in the same laboratory by the same operator using the same equipment within short intervals of time. Moreover, this study was designed to evaluate changes of the dermoscopic morphology of the irradiated nevi based on a panel of criteria described by Hofmann-Wellenhof *et al.*<sup>4</sup> During the three study visits, target nevi will be documented by digital close-up and dermoscopic images in order to prospectively assess the following 10 dermoscopic parameters on a visual analogue scale from 0 to 10 (0 indicates 'parameter absent' and 10 indicates 'parameter prominently present', unless otherwise noted): (1) asymmetry, (2) border (sharp, 0; faded, 10), (3) erythema in the nevus, (4) telangiectasia in the nevus, (5) pigmentation, (6) hypopigmented areas, (7) pigment network, (8) sharpness of pigment network (sharp, 0; faded, 10), (9) regularity of pigment network (irregular, 0; regular, 10) and (10) brown-black globules.

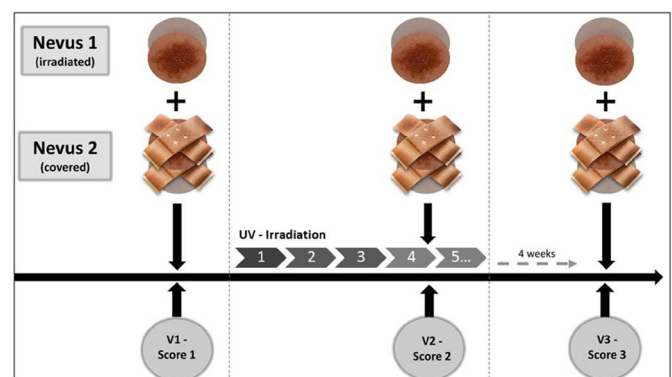
### Study population and criteria for inclusion/exclusion

A total of 50 fully evaluable patients with the medical indication for elective phototherapy in the department of dermatology, University of Heidelberg, and at least 18 years of age shall be included. Eligible patients must show at least two common nevi in the same body area showing similar size and shape. Furthermore, the two nevi intended for EIS analysis need to show the following characteristics: diameter between 2 and 20 mm; intact skin surface (ie, non-ulcerated and non-bleeding lesional skin); absence of scarring or fibrosis consistent with

previous trauma; located outside of hair-covered areas or areas containing foreign matter (eg, tattooed skin areas). Moreover, both nevi for EIS analysis must not be located at special anatomic sites (ie, acral skin, genitalia, conjunctival or mucosal skin). Additionally, the two nevi intended for EIS analysis need to be located in an unaffected area with healthy skin and clear absence of inflammatory skin changes (ie, no signs of psoriasis, eczema, acute sunburn or similar lesional skin changes). Patients who are not able to read, understand or sign the study-specific informed consent form shall also be excluded from this study.

### Methods

This study was designed to evaluate the effects of UV irradiation on the score of electrical impedance spectroscopy measurements of nevi in 50 patients. Clinical investigators will select two nevi in the same body area of patients scheduled for phototherapy. Next, one nevus (nevus 1) in each patient is exposed to UV radiation, while a second nevus (nevus 2) of similar size and located at the same body area is covered with a UV-shielding sticker. The initial radiation dose is individually determined based on the patient's skin phototype. The patients receive several treatments per week with increasing UV doses as tolerated depending on the underlying disease and routine phototherapy protocols. EIS scores of the irradiated nevus (nevus 1) and the non-irradiated nevus (nevus 2) will be evaluated in three study visits: visit 1, before start of phototherapy; visit 2, during phototherapy and after at least four treatment sessions and visit 3, after termination of phototherapy and not earlier than 4 weeks after last irradiation. Our main analysis is based on the first two study visits (visit 1 and visit 2). The follow-up visit after termination of phototherapy (visit 3) is used in a secondary analysis to investigate the time to a normalisation of UV-induced EIS changes. Moreover, for each lesion and time-point, two consecutive measurements will be performed to assess the EIS repeatability and variance of EIS scores not related to UV exposure (see [figure 1](#)). All EIS measurements in this study will be performed with the Nevisense system (Scibase, Stockholm, Sweden). This category II device is eligible for the assessment of a restricted number of atypical, preselected lesions.<sup>1</sup> After moisturising the skin, a probe with an electrode and



**Figure 1** Flow chart of the study. UV, ultraviolet.

gold-covered pins is pressed to the melanocytic lesion of interest. A reference measurement of healthy skin close to the lesion will be obtained before the lesion measurement. A single measurement takes approximately 10 s and is painless and non-invasive. The system computes both a score (0–10) and a dichotomous output (EIS negative with scores <4/positive with scores  $\geq 4$ ), reflecting the degree of atypia identified. The recommended fixed cut-off at a score of 4 is based on an algorithm developed with data from multiple clinical studies.<sup>2</sup> The observed sensitivity and specificity of the device was reported at 96.6% and 34.4%, respectively.<sup>2</sup> Irradiation will be performed with either a UV-A1 lighting tube (spectrum 350–400 nm and a maximum of 370 nm) or a combination of UV-A and UV-B lighting tubes, which show a spectral radiation distribution of 280–410 nm and a maximum of 351 and 306 nm (Herbert Waldmann GmbH & Co. KG, Villingen-Schwenningen, Germany), respectively.

### Statistical analysis

All end points and patient characteristics will be analysed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, means, SD, medians and first and third quartiles as well as either minimum and maximum or absolute and relative frequency will be reported. In the primary analysis, we will examine the extent of increase or decrease in EIS scores of nevi from visit 1 to visit 2. This change will be compared between the cases undergoing the UV irradiation and the control cases using a linear regression model where the baseline value (V1), age and gender of the patient will be included as predictors. We will provide an estimate of the (adjusted) mean difference between the two groups with a 95% CI and the associated P value. Box plots will be used to visualise the findings. In a secondary analysis, the same model will be applied for the change from visit 1 to visit 3 and from visit 2 to visit 3. In addition, we will apply repeated measures analysis of variance where all visits will be included. Age and gender of the patients will again be included as covariates. In the analysis of reproducibility of EIS measurements (two measurements of the same lesion in a row under the same conditions), the intraclass correlation coefficient will be estimated. To analyse the changes in the dermoscopic appearance of nevi, we will provide estimates for the difference in the numerical scores for the grade of 10 different dermoscopic parameters (see above) after UV irradiation with 95% CIs and P values. Missing values will be imputed via the baseline observation carried forward approach. In a sensitivity analysis, we will conduct a complete case analysis.

### Sample size calculation

As this is a first pilot study investigating the effect of UV irradiation on EIS measurements, a formal sample size calculation is neither applicable nor feasible. However, a sample size of 50 complete and evaluable data sets is sufficient to detect a Cohen's effect size of 0.4 (with a power of

0.8 and a significance level of 0.05) in the primary analysis where the potential impact of UV irradiation on the EIS score is evaluated when applying an unpaired t-test. The adjustment for covariates in a linear regression model typically increases the power. Taking into account a dropout rate of 20%, the recruitment of 63 patients should result in an overall sample size of 50 complete data sets.

### Ethical considerations and regulatory obligations

The information contained in this protocol and the implementation of the study are consistent with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (2013), the principles of International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines (E6) and the current laws. Before initiation of the study, the protocol was presented to the independent ethics committee of the medical faculty of the University of Heidelberg. Ethics approval was granted by the ethics committee in June 2017 (ethics approval number S-279/2017). The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure. The participant should read and consider the statement before signing and dating the informed consent form. The names of patients and all confidential data are subject to professional discretion and the 'Bundesdatenschutzgesetz (BDSG)'. Processing of medical data will only take place in pseudonymous form. Third parties will not be allowed access to patient data. There is no personal benefit and no additional risks for study participants.

**Contributors** CF, AS, LU and HAH participated in the development and the implementation of the study (writing of the protocol, submission to ethics committee, data management) and helped to draft and to review the manuscript. All authors read and approved the final version of the manuscript.

**Competing interests** None declared.

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