




BMJ Open MEDEA randomised intervention study protocol in Cyprus, Greece and Israel for mitigation of desert dust health effects in adults with atrial fibrillation

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ABSTRACT

Introduction Mediterranean countries experience frequent desert dust storm (DDS) events originating from neighbouring Sahara and Arabian deserts, which are associated with significant increase in mortality and hospital admissions, mostly from cardiovascular and respiratory diseases. Short-term exposure to ambient air pollution is considered as a trigger for symptomatic exacerbations of pre-existing paroxysmal atrial fibrillation (AF) and other types of heart arrhythmia. The Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches clinical randomised intervention study in adults with AF is funded by EU LIFE+programme to evaluate the efficacy of recommendations aiming to reduce exposure to desert dust and related heart arrhythmia effects.

Methods and analysis The study is performed in three heavily exposed to desert dust regions of the Eastern Mediterranean: Cyprus, Israel and Crete-Greece. Adults with paroxysmal AF and implanted pacemaker are recruited and randomised to three parallel groups: (a) no intervention, (b) interventions to reduce outdoor exposure to desert dust, (c) interventions to reduce both outdoor and indoor exposure to particulate matter during desert dust episodes. Eligible participants are enrolled on a web-based platform which communicates, alerts and makes exposure reduction recommendations during DDS events. Exposure changes are assessed by novel tools (smartwatches with Global Positioning System and physical activity sensors, air pollution samplers assessing air quality inside and outside participant's homes, etc). Clinical outcomes include the AF burden expressed as the percentage of time with paroxysmal AF over the total study period, the incidence of ventricular arrhythmia episodes as recorded by the participants' pacemakers or cardioverters/defibrillators and the disease-specific Atrial Fibrillation Effect on Quality-of-Life questionnaire.

Ethics and dissemination Local bioethics' authorities approved the study at all sites, according to national legislations (Cyprus: National Bioethics Committee, Data Protection Commissioner and Ministry of Health; Greece,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Throughout the study, personal monitoring through wearable sensors assesses the compliance of adults with atrial fibrillation (AF) to recommendations aiming to reduce the exposure to desert dust storms (DDS).
- ⇒ Air cleaning devices continuously filter indoor air in homes of adults with AF during DDS events.
- ⇒ Personalised assessment reduces the risk of exposure misclassification.
- ⇒ The study uses validated tools to assess health outcomes, including AF burden and quality of life.
- ⇒ Advanced age and/or other comorbidities (eg, impaired vision) of study participants may compromise the use of wearable devices and smartphones.

Scientific Committee and Governing Board of the University General Hospital of Heraklion; Israel: Institutional Review Board ('Helsinki committee') of the Soroka University Medical Center). The findings will be publicised in peer-reviewed scientific journals, in international conferences and in professional websites and newsletters. A summary of the results and participants' interviews will be included in a documentary in English, Greek and Hebrew.
Trial registration number ClinicalTrials.gov Identifier; NCT03503812.

INTRODUCTION

Exposure to air pollution is a well-established risk factor for cardiorespiratory morbidity and mortality.^{1 2} Among other outcomes, exposure to particulate matter (PM) is associated with higher incidence of cardiac infarction³ and ventricular arrhythmias.⁴ Furthermore, ambient air pollution is also associated with atrial fibrillation (AF), the most common heart rate disturbance, affecting almost 2% of the population worldwide, and a known risk



factor for heart failure, stroke, hospital admission and mortality.^{5–8}

Although the evidence on the relationship between PM and incidence of heart arrhythmias comes from studies of anthropogenic particulate pollution (road traffic, industry, etc), particulate pollution in urban settlements may have substantial contributions from non-anthropogenic sources, such as desert dust storms (DDS).⁹ This is very common for regions with geographical proximity to the global desert dust belt, such as the Mediterranean basin. In Mediterranean countries, DDS events may appear in more than 15% of the days of the year with the greater frequency and intensity of the events recorded in the south-eastern Mediterranean.^{10 11}

Despite the natural origin of DDS events, recent evidence supports their strong association with adverse health outcomes such as increased all-cause and cause-specific mortality and morbidity.^{12–16} Even though, direct evidence linking the incidence of AF episodes with DDS exposure is still lacking, recent studies have identified short term exposure to ambient air pollution as a trigger for AF episodes.^{17–19}

The current public health strategy across many countries during anthropogenic high pollution events is to issue alerts or warnings to the population, targeting vulnerable groups such as the known cardiac patients. These alerts usually are accompanied by recommendations to avoid vigorous outdoor activity and stay indoors during the events.^{20 21} Although there is a well-established rationale behind these recommendations,²² adherence has been found to vary widely, depending on several personal and other parameters.²³ In the case of DDS events, a similar strategy of alerts and recommendations is followed on their appearance,²⁰ but to date, there is no real-life evidence supporting the efficacy of these recommendations in reducing personal exposure to dust, either in the outdoor or the indoor environments, not or their role in mitigating the related health risks.

The ‘Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches (MEDEA) Atrial Fibrillation study’ has been designed to study the feasibility and effectiveness of simple exposure reduction recommendations (including behavioural changes with/without indoor air cleaners vs no intervention) in a randomised cohort of AF patients in parallel groups during DDS events in South-Eastern Mediterranean countries. This behavioural intervention study will quantify the impact of these recommendations both in terms of change in personal exposure to air pollution and in terms of AF burden reduction and improvement in health-related quality of life (HRQoL). The project is carried out by an eight-partner consortium across three heavily DDS-exposed sites in the Eastern Mediterranean, Cyprus, Israel and Crete-Greece. The study benefits from a series of novel environmental exposure assessment tools such as smartwatches equipped with Global Positioning System (GPS) and physical activity sensors that enable the objective assessment of personal compliance to the

recommendations, while the availability of air pollution samplers allows the quantification of outdoor and indoor air pollution exposure among the study population.

METHODS AND ANALYSIS

The Standard Protocol Items: Recommendations for Interventional Trials checklist has been used for this report.²⁴

Population

The target population is men and women with AF and previously implanted dual lead (atrial and ventricular) pacemaker or implantable cardioverter defibrillator (ICD), who attend the heart arrhythmia clinics at Nicosia General Hospital in Cyprus, Soroka Clinical Research Center in Beer-Sheba, Israel and University Hospital of Heraklion, Crete, Greece. Additional details on the recruitment of participants are provided in online supplemental material. Screening of the AF patients at each site started in Fall 2018 and Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches (MEDEA) personnel continues to identify and follow-up eligible AF patients throughout the three follow-up periods in 2019, 2021 and 2022. The SPIRIT flow diagram for the AF study is presented in figure 1.

Eligibility criteria

Eligible for the study are patients with permanent atrial or dual chamber pacemakers or ICDs implanted at least 2 months prior to randomisation, with:

1. History of paroxysmal AF.
2. Detection of AF episodes in pacemaker/ICD monitoring of >6 min in duration.

The study puts no limitations on patients’ medication regimens during the study period.

Exclusion criteria are permanent AF, reversible causes of AF (eg, hyperthyroidism), inability to understand and use study tools (smartphones, software applications), active smoking, terminal illness or not living at least 5 days per week in the same household.

Study design

Patients are randomised with a 1:1:1 ratio, using a random assignment tool, into three parallel groups: *group 1*: no additional intervention during DDS (‘business as usual’ scenario), *group 2*: interventions for outdoor exposure reduction, *group 3*: combined interventions for both outdoor and indoor exposure reduction. The study design offers the opportunity to assess (a) outdoor exposures to PM, (b) indoor exposures to PM and (c) related health outcomes in three parallel groups during the same events of DDS with and without intervention measures.

Study interventions and recommendations

To reduce the outdoor and indoor exposure to DDS pollution, relevant recommendations have been developed. In brief, for outdoor exposure reduction intervention, it is recommended to the participants to stay

in group 3. In order to enhance uptake and acceptability of the recommendations, we produced relevant audiovisual spots with animated guidelines in Greek, Hebrew and English languages. The English version for the outdoor exposure reduction intervention (group 2, online supplemental video S1) and for the outdoor and indoor exposure reduction intervention (group 3, online supplemental video S2) are available in online supplemental material.

MEDena Health-Hub

For the purposes of the project, a patient-centred web-based platform (the MEDena Health-Hub) and a smart phone application (the MEDEApp) have been developed. These tools receive input from existing models that forecast DDS events in the countries that take part in the study and provide alerts to participants and researchers with the appearance of DDS events through text messaging and smartphone applications, coupled with relevant exposure reduction recommendations (personalised to each participant, according to the randomisation group, they belong—group 1, 2 or 3). The forecasting models for desert dust rely on the transport scheme of the desert dust, the proximity of the given area to the desert source and other factors.²⁵ The platform algorithm takes into account these forecasts for DDS and issues alert to participants based on increased PM concentrations (including both particles of desert dust and anthropogenic origin) compared with site-specific background levels as described previously.²⁶ Of note, so far, there is no well-established classification system for DDS severity, thus the forecasting models and alert algorithms treat all DDS events equally.²⁷

Using cloud technologies, the above-mentioned tools offer the opportunity to store health and exposure data from all participants (groups 1, 2 and 3), as these are recorded through the wearable sensors and online questionnaires.

Following randomisation, participant's sociodemographic characteristics, medical and medication history as well as information on household location and characteristics, are uploaded to the MEDena Health-Hub. In addition, a wearable sensor (EMBRACE smartwatch (Embrace Tech LTD, Cyprus) is provided to the participant, who is asked to wear it daily throughout the study period, except during bedtime, bathing and swimming. The study personnel are responsible to train the AF patients in the tools and procedures to be followed during the study. A leaflet with instructions on the use of the EMBRACE smartwatch and MEDEApp is also provided to the participants. Additional details on the MEDena Health-Hub and MEDEA App have been published previously.²⁶

Exposure assessment

1. Wearable sensors: physical activity as well as time spent outdoors are assessed by the sensors of the EMBRACE smartwatch. The smartwatch is supplied with GPS, which records continuously the time the participant

spends indoors and outdoors, and activity tracking (pedometer) hardware and software, which records steps and heart rate. In addition, the smartwatch also includes an embedded sim card and Wi-Fi connectivity and can be used as a stand-alone device. Finally, the software can synchronise the sensors, so that data are transferred to the cloud database marked with the same timestamp.

2. Air pollution sensors: particle samplers (Harvard High Volume Cascade Impactors, Harvard University, USA) are placed outside and inside representative participants' houses. Furthermore, indoor, commercial low volume air quality sensors (OPC-N3 Optical Particle Counters, Alphasense, United Kingdom) are used to assess the levels of indoor exposure to PM across the three intervention groups. The indoor and outdoor particle samplers use Teflon filters which are analysed to give the concentrations of PM₁₀, PM_{2.5}, black carbon and elements inside and outside representative houses during DDS and DDS-free days.
3. Questionnaires: each participant is asked to complete an activity questionnaire following each DDS event, which assesses the reported compliance to the recommendations. A schematic of the AF study is presented in [figure 2](#).

The recordings of wearable GPS and activity sensors are coupled with the measurements collected from the air pollution samplers and the questionnaires to provide a much higher spatiotemporal accuracy for personal air pollution exposure and an estimate of the compliance to the intervention. To ensure minimal technical problems with the wearables and devices, as well as to facilitate the compliance of the participants, we maintain an extended support system characterised by frequent communication with participants and their families and implement simple and cost-effective setting adjustments to the device to ensure systematic activation of the data collection application at regular time intervals, increase battery duration and facilitate uninterrupted operation of smartwatch background process.²⁸

Baseline and follow-up clinical assessments

Eligible AF patients after screening are invited for a baseline clinical assessment, which includes detailed questions on sociodemographic characteristics, health symptoms, particularly heart arrhythmias symptoms, utilisation of medical care, medication history and household environmental characteristics, including tobacco smoke exposure. A baseline assessment of the AF/ventricular arrhythmia episodes is obtained after downloading relevant data from the participants' pacemakers or ICDs.

Follow-up periods span for 6 months and include monitoring of the daily location and physical activity of AF patients using the smartwatches. Phone interviews at baseline and then at every 1 month throughout the follow-up period are performed collecting information on heart arrhythmia symptoms control, medication use, unscheduled visits to health professional for arrhythmias

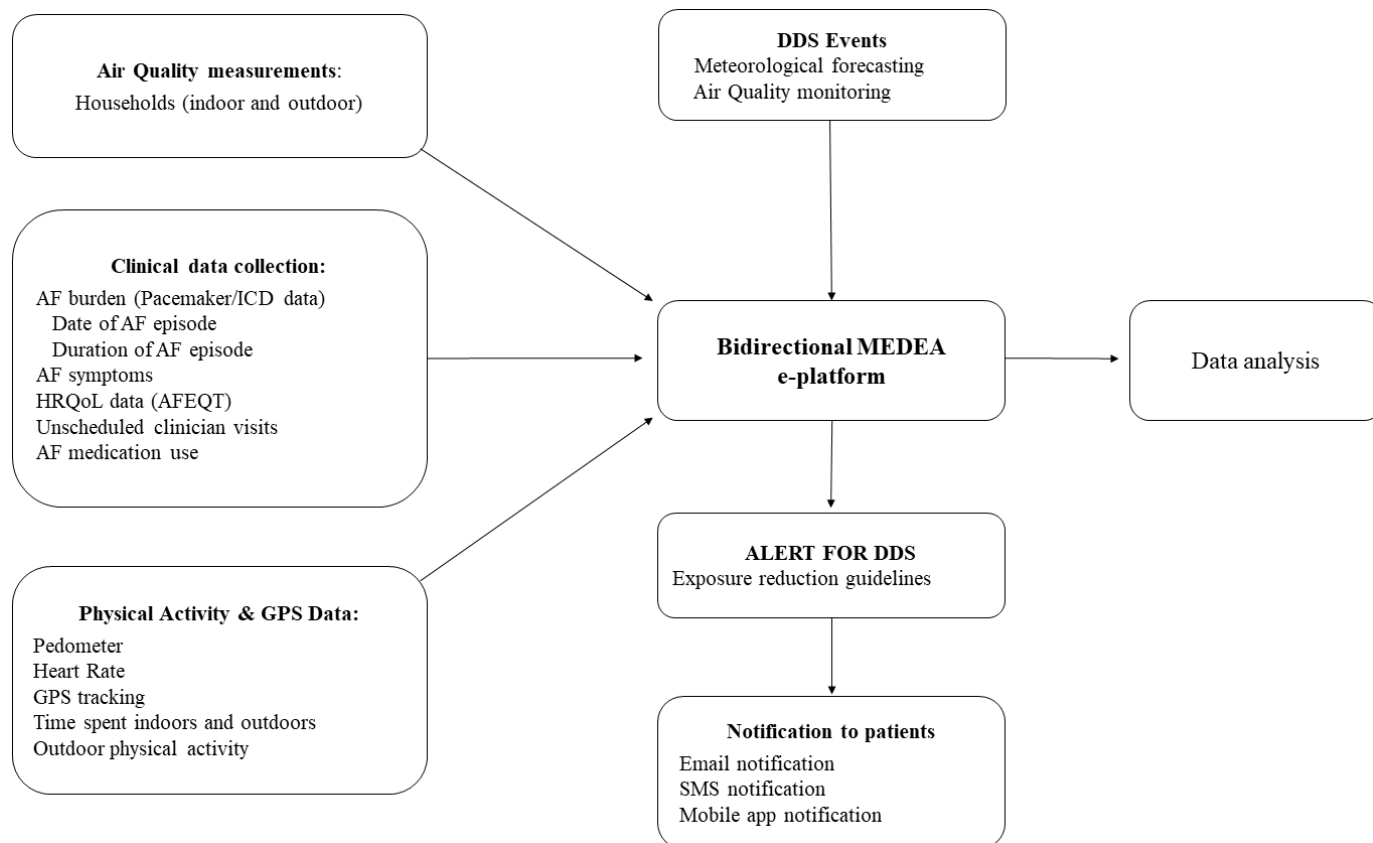


Figure 2 MEDEA atrial fibrillation study schematic diagram. The bidirectional MEDEA Health-Hub is updated with meteorological forecasting and air-quality information regarding DDS events and sends alerts and exposure reduction guidelines to AF patients. At the same time, the cloud database is automatically collecting the physical activity and GPS data from the smartwatches worn by the participants. Researchers also manually upload participants' clinical data and air quality measurements. AF, atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality of Life questionnaire; DDS, Desert Dust Storm; GPS, global positioning system; HRQoL, Health Related Quality of Life; SMS, short messaging service text message.

and health-related quality of life using the Atrial Fibrillation Effect on Quality-of-Life (AFEQT, license number: 20171404) questionnaire.²⁹ Incidence of AF/ventricular arrhythmia episodes is recorded daily using the already implanted participants' pacemaker or ICD during the follow-up period. The recorded episodes are downloaded by interrogation of the pacemaker or ICD after the end of the study period during a visit to the Hospital Arrhythmia Clinic. The timeline and description of baseline and follow-up assessments in the AF panel study are presented in figure 3. Non-participation to the clinical visits was the only reason for discontinuation of the study participation. Additional details on the intervention implementation are provided in online supplemental material.

AF outcomes and data analysis

The primary health outcome in the study is the reduction in the AF burden defined as the percentage of time with AF during the whole study period. A 20% reduction in the AF burden is considered as clinically significant. For the primary analysis, we will compare the combined effect in the two intervention groups versus the control group. Next, we will make comparisons between each of the intervention groups and the control group and between the intervention groups. Furthermore, for

HRQoL, changes equal or greater than (\pm) five points in the AFEQT questionnaire score are considered clinically significant. Other health outcomes include the presence or absence of arrhythmia symptoms in the prior 4-week period, heart rate variability, arrhythmia medication use and unscheduled hospital visits for heart arrhythmias. Apart from the health outcomes, the exposure reduction across the intervention groups will be assessed as an outcome of this study, estimating directly the compliance and the effectiveness of the recommendations.

1. Sample size calculation: there are no studies that evaluated the reduction in AF burden attributed to the reduction in exposure to ambient air pollution. Nevertheless, assuming a mean follow-up period of 6 months and an effect size of 20% change in the outcome, a study sample size of 118 is required to demonstrate a statistically significant result. This number is estimated for performing a two-way repeated measures Analysis of Variance (ANOVA) statistical test for the comparison of the intervention and control groups and assuming an alpha value at 0.05, power of 80% and a 50% correlation between repeated measurements.
2. Statistical analysis plan: descriptive statistics will be presented using summaries of key variables in the form of

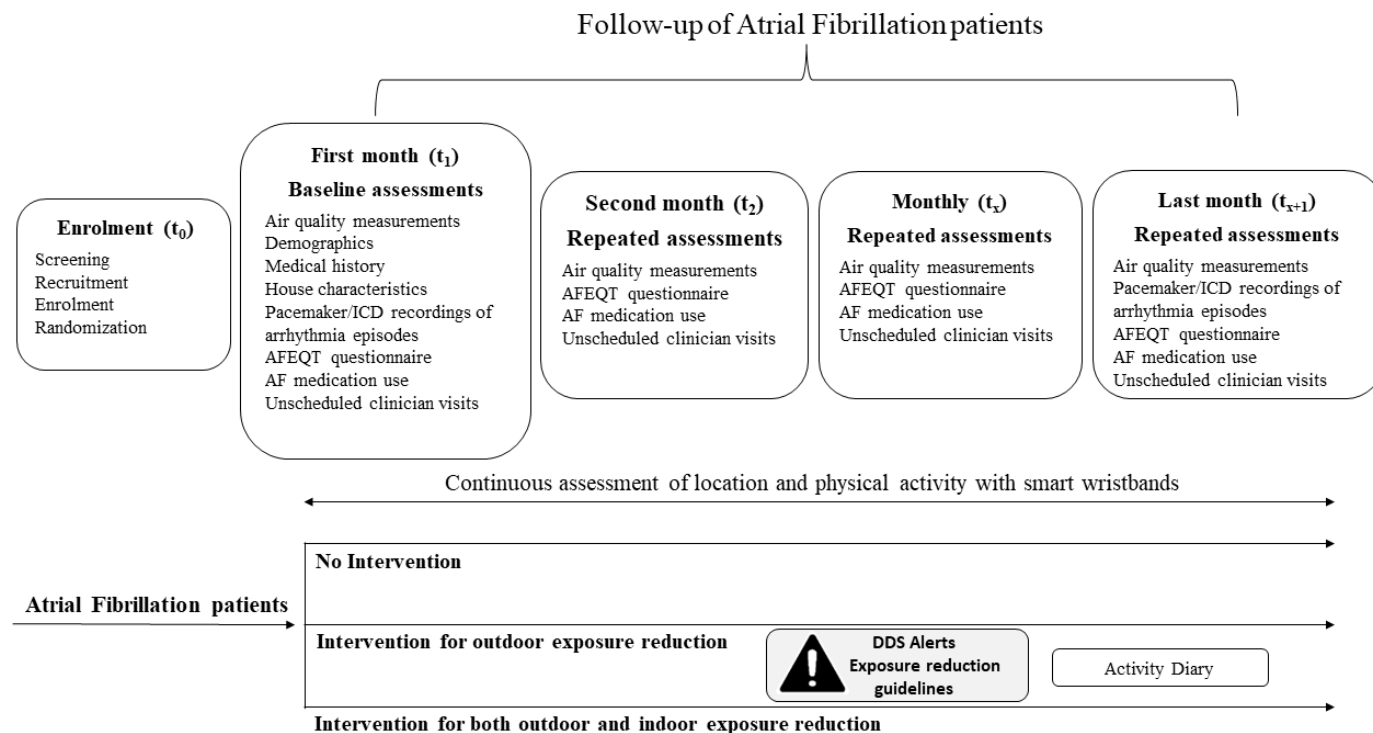


Figure 3 MEDEA atrial fibrillation study assessments timeline. Timeline of baseline and follow-up assessments in atrial fibrillation panel study. AFEQT, Atrial Fibrillation Effect on Quality of Life questionnaire; DDS, Desert Dust Storm; GPS, global positioning system; HRQoL, Health Related Quality of Life; ICD, implantable cardioverter defibrillator.

mean (SD) and median (range) for normally and non-normally distributed variables, respectively. For categorical variables, the distribution in percentages will be presented. Comparisons between intervention and control groups will be carried out using the two-way repeated measures ANOVA statistic test for continuous variables and the χ^2 test for categorical variables. The statistical analysis plan for the impact of intervention on exposure will include the estimation of the fraction of outdoor particles that penetrate indoors and remain suspended using the infiltration factor approach as described previously³⁰ and will employ multiple linear regression models to quantify the effect of intervention measures on indoor PM levels. The statistical analysis for the impact of intervention on HRQoL (AFEQT score) will rely on a linear mixed effects (hierarchical) regression model, which will include fixed effects for intervention group and subject-specific random intercepts. The model will be adjusted for several covariates including age, gender, year of study, site of study and climatic factors.

ETHICS AND DISSEMINATION

The MEDEA AF panel study has been approved by national authorities at all sites. In Cyprus, approvals have been obtained from the Cyprus National Bioethics Committee (EEBK EPI 2017.01.141), by the Data Protection Commissioner (No. 3.28.223) and Ministry of Health (No 5.34.01.7.2E). In Greece, approvals have been obtained from the Scientific Committee (25/04/2018,

No: 1748) and the Governing Board of the University General Hospital of Heraklion (25/22/08/2018). In Israel, approval has been obtained from the Institutional Review Board ('Helsinki committee') of the Soroka University Medical Center (No 0374-17-SOR). Participants sign the informed consent from the corresponding centre at recruitment. The study has been registered and approved by the clinicaltrials.gov online repository.

Dissemination plan

The study findings will be disseminated according to the predefined dissemination plan of the LIFE MEDEA project. The project dissemination plan includes publication of the study findings in international peer-reviewed scientific journals, as well as international scientific conferences, with authorship eligibility as defined by the International Committee of Medical Journal Editors recommendations. In addition, the findings will be also communicated to the scientific community, regulatory authorities, patient organisations and the general public through publication of a series of short-piece articles for professional websites and newsletters as well as through the organisation of educational activities and open public fairs in the three study sites. Finally, the LIFE MEDEA project dissemination plan also includes the production of 50 min documentary with a summary of the study findings that will be made available in English, Greek and Hebrew languages. The anonymised study data set and the statistical code will be made available online in an appropriate, open access, public repository.

Patient and public involvement

The above-mentioned documentary will include interviews from study participants and participating clinicians reporting their experiences during the study.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All information relevant to the study protocol in included in the manuscript and the supplementary material, and also is publicly available at the trial registry (ClinicalTrials.gov Identifier: NCT03503812). By the completion of data analysis and in order to publish the results, data will be uploaded on a public, open access repository.

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