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The MEDEA randomized intervention study protocol for mitigation of desert dust health effects in adults with atrial fibrillation

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Title: The MEDEA randomized intervention study protocol for mitigation of desert dust health effects in adults with atrial fibrillation

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ABSTRACT (299 words)

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 MEDEA clinical randomised intervention study in adults with AF is funded by EU LIFE+ program 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 randomized 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 desert dust. 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 GPS and physical activity sensors, air pollution samplers assessing air quality inside and outside participant's homes, etc). Primary 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 (AFEQT) questionnaire.

Ethics and dissemination:

Local bioethics' authorities approved the study at all sites, according to national legislations. The findings will be publicised in peer-reviewed scientific journals, in international conferences, and in

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professional websites and newsletters. A summary of the results and participants' interviews will be included in a documentary in English, Greek and Hebrew.

Registration details: ClinicalTrials.gov Identifier: NCT03503812, April 18, 2019

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study will assess for the first time, the compliance of a vulnerable population group to commonly issued recommendations for reduction of exposure to Desert Dust Storm (DDS) using personal monitoring through wearable sensors.
- The study will assess the impact of using air cleaning devices on indoor air quality in homes of adults with Atrial Fibrillation (AF) during DDS events.
- The study will use validated tools to assess a series of health outcomes including AF burden and disease-specific health-related quality of life.
- AF patients are often of advanced age and may be constrained by other co-morbidities (e.g. impaired vision) that may compromise the use of wearable devices and smartphones.

Key words: Desert Dust, Asian Dust, Atrial Fibrillation, Public Health Intervention, Sensors

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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 is associated with higher incidence of cardiac infarction [3] and ventricular arrythmias [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 particulate matter 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

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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 "MEDEA (Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches) Atrial Fibrillation study" has been designed to study the feasibility and effectiveness of simple exposure reduction recommendations (including behavioural changes and/or use of 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 interventional 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.

METHODS AND ANALYSIS

The SPIRIT checklist has been used for this report [24].

Population

The target population are 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 (SCRC) in Beer-Sheba, Israel and University Hospital of Heraklion, Crete, Greece. Additional details on the recruitment of participants are provided in Supplementary Material. Screening of the AF patients at each site started in Fall 2018 and 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

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

a. History of paroxysmal AF and

b. 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, terminal illness, or not living at least 5 days per week in the same household.

Study design

Patients are randomized 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 indoors, and avoid any intense physical activity outdoors, competitive sports and unnecessary walks (Group 2 & Group 3). For indoor exposure reduction intervention, it is recommended to close doors and windows, to seal possible openings around doors and windows minimizing outdoor air penetration, and to filter indoor air by using continuously an air cleaning device (Coway Storm 1516D, Coway, South Korea, see Supplementary Material for further details). Indoor exposure reduction measures were implemented at the households of the participants 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

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reduction intervention (Group 2, Video S1) and for the outdoor and indoor exposure reduction intervention (Group 3, Video S2) are available in Supplementary Material.

MEDena® Health-Hub

For the purposes of the project, a patient-centered 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, coupled with relevant exposure reduction recommendations (personalized to each participant, according to the randomization group they belong). Also, by using cloud technologies, they offer the opportunity to store health and exposure data from all participants, in the intervention and control groups, as these are recorded through the wearable sensors and online questionnaires.

Following randomization, participant's socio-demographic 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 [25].

Exposure assessment

i. Wearable sensors: Physical activity as well as time spent outdoors are assessed by the sensors of the EMBRACE™ smartwatch. The smartwatch is supplied with global positioning system (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. Lastly,

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the software can synchronize the sensors, so that data are transferred to the cloud database marked with the same timestamp.

ii. 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 PM_{10}, $PM_{2.5}$, black carbon (BC) and elements inside and outside representative houses during DDS and DDS-free days.

iii. Questionnaires: Each participant is asked to complete an activity questionnaire following each DDS event, which assesses the reported compliance to the recommendations. A schematic diagram of the AF study is presented in Figure 2.

Baseline and Follow-up Clinical Assessments

Eligible AF patients after screening are invited for a baseline clinical assessment, which includes detailed questions on socio-demographic characteristics, health symptoms, particularly heart arrhythmias symptoms, utilization 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 and health related quality of life using the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT, license number: 20171404) questionnaire [26]. Incidence of AF/ventricular arrhythmia episodes is recorded daily using

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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 Supplementary Material.

Atrial fibrillation outcomes and data analysis

The primary health outcome in the AF clinical study is a 20% reduction in AF burden defined as the percentage of time with AF during the whole study period. 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 health-related quality of life, changes equal or greater than (±) 5 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, arrhythmia medication use and unscheduled hospital visits for heart arrhythmias.

i. 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 follow-up period for 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 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.

ii. Statistical analysis plan: Descriptive statistics will be presented using summaries of key variables in the form of mean (standard deviation) 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 Chi-Square test for categorical

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variables. The statistical analysis for the impact of intervention on health-related quality of life (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 (ΕΕΒΚ ΕΠ 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 center at recruitment. The study has been registered and approved by the clinicaltrials.gov online repository (ClinicalTrials.gov Identifier: NCT03503812)

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 organizations and the general public through publication of a series of short-piece articles for professional websites and newsletters, as well as through the organization of educational activities and open public fairs in the three study sites. Lastly, the LIFE MEDEA project dissemination plan also includes the production of 50-minute documentary with a summary of the study findings that will be made available in English, Greek and Hebrew languages. The anonymised study

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dataset 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.

DISCUSSION

The MEDEA Atrial Fibrillation panel study represents the first comprehensive effort to assess the efficacy of simple and sustainable recommendations in reducing exposure to desert dust and mitigating associated health effects among a susceptible population subgroup, such as the AF patients. The study benefits from a series of novel environmental exposure assessment tools such as smartwatches equipped with GPS and physical activity sensors that enable the objective assessment of personal compliance to the recommendations, while the availability of indoor and outdoor air pollution samplers allows the quantification of outdoor and indoor air pollution exposure among the study population.

In the past, several studies focusing on air pollution health effects were characterised by important misclassifications in exposure assessment. More specifically, exposure to air pollutants was estimated based on measurements carried out at central air quality monitoring stations that are usually sparsely distributed across the urban environment and may not adequately represent the variability of air pollution exposures across residential areas [27]. In addition, reliance on ambient air quality monitoring stations presumes that outdoor air pollution levels constitute an appropriate proxy for overall air pollution exposure. However, in these approaches, information on indoor air pollution concentrations is not taken into account and as a result, the risk for exposure misclassification is high [28-30]. Furthermore, in several previous studies, investigators relied on residential addresses to estimate personal exposure estimates without taking into consideration the participants' daily activity and mobility profile [31-33]. In the present study, we rely on a combination of indoor and outdoor samplers

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in representative premises and installation of commercial low volume air quality sensors across the three intervention groups to estimate air pollutant concentrations at the residential level without relying on the air quality monitoring network at the three sites. Moreover, the use of wearable GPS and activity sensors for the continuous and objective assessment of the physical activity levels and the time participants spend indoors and outdoors can be coupled with the measurements collected from the indoor and outdoor air pollution samplers to provide a much higher spatiotemporal accuracy for personal air pollution exposure. Collectively, the employed methods allow for the objective assessment of personal compliance to MEDEA recommendations, while at the same time the risk for exposure misclassification in air pollution exposure estimates due to uncertainties related to the variability of human mobility and lack of information on indoor air pollution levels are significantly reduced.

Similarly, health effects of desert dust exposure are usually relying on administrative and retrospective data, employing an ecological study design. These data are usually restricted to deaths or hospital admissions, emergency department visits and outpatient clinics' visits [12-16]. However, these morbidity metrics may be influenced by subjective health care seeking behavior and are not adequate for the evaluation of the onset, duration and severity of an outcome [34]. In the MEDEA AF panel study, we assess prospectively a range of clinical outcomes in both the control and interventions groups. In particular, the AF panel study benefits from the analysis of arrhythmia recordings downloaded from previously implanted pacemakers, enabling us to determine the start and duration of all events, even the asymptomatic ones. In addition, the systematic collection of data on additional outcomes such as disease specific HRQoL, offers the possibility to address additional aspects of the patient's wellbeing and whether these can be improved as a result of the MEDEA recommendations.

One of the main and earliest challenges of the project, was the need to ensure data accuracy and reliability through the selection of an appropriate wearable device. Usage of smart devices requires a certain degree of technological literacy, which is challenging, especially in the older population of the AF patients. In addition to age-group applicability, among other criteria, the memory capacity and energy efficiency of the device had also to be considered, as these may affect the credibility of the collected data [35]. In order to overcome this issue, we evaluated several commercially available smart

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watch devices and we chose the LEMFO-LM25 smartwatch equipped with the EMPBRACE™ software (Embrace Tech LTD, Cyprus). This smartwatch does not require manual synchronization with another device but acts as a stand-alone device that is able to upload data automatically when it gets in contact with the WI-FI network at the participant's house. Nevertheless, as recent systematic reviews demonstrated, although commercial smartwatches are overall valid instruments for monitoring activity and behavior, limitations such as poor suitability for elderly users, as well as battery, memory and data quality issues are usually present [36, 37]. To address these inherent limitations, we maintain an extended support system characterized 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 ensure uninterrupted operation of smartwatch background process.

Finally, we faced another important challenge, as several older types of pacemakers implanted to AF patients did not store more than 16 arrhythmia episodes. Thus, for the performance of the AF panel study we rely mainly on patients with implanted ICD's or modern pacemakers such as Advisa (Advisa DR MRI™ and Advisa SR MRI™, Medtronic, United States) and Adapta (Adapta DR™ and Adapta SR™, Medtronic, United States). These pacemakers save all fast rate episodes, regardless of the time interval between interrogations of the device. Furthermore, AF patients are quite often in advanced age and have other limiting co-morbidities such as impaired vision and arthritis, which may pose difficulties on the use of the wearable devices and the touchscreen of smartphones. These unforeseen problems significantly reduced the number of available patients for recruitment at all study sites and as a contingency measure, we have intensified recruitment efforts and expanded recruitment in smaller additional arrhythmia clinics in Cyprus.

LIST OF ABREVIATIONS

DDS – Desert Dust Storms

PM_{10} – Particulate Matter <10 μm

$PM_{2.5}$ – Particulate Matter <2.5 μm

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AF – Atrial Fibrillation

GPS – Global Positioning system

BC – Black Carbon

ICD – Implantible Cardioverter-Defibrillator

AFEQT – Atrial Fibrillation Effect on Quality of Life

AUTHORS' COMPETING INTERESTS

The authors declare no conflict of interest

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AUTHORS CONTRIBUTIONS

PK: Methodology, Investigation, Software, Data curation, Project Administration Writing-Original draft preparation; **SIP**: Conceptualization, Methodology, Data curation, Writing-Original draft preparation; **MGK**: Data Curation, Investigation, Visualisation, Writing - Review & Editing; **NM**: Methodology, Writing - Review & Editing; **IP**: Data curation, Investigation, Writing – Review & Editing; **VN**: Conceptualization, Methodology, Writing - Review & Editing, Project Administration; **ES**: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing; **GS**: Conceptualization, Data Curation, Software, Visualisation, Writing - Review & Editing; **CK**: Visualisation, Resources, Writing - Review & Editing; **ER**: Conceptualization, Data Curation, Software, Visualisation, Writing - Review & Editing; **FT**: Conceptualization, Methodology, Resources, Software, Writing - Review & Editing; **CS**: Conceptualization, Methodology, Resources, Writing -

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Review & Editing; **KP**: Conceptualization, Methodology; Software, Validation, Resources, Writing - Review & Editing; **PKY**: Conceptualization, Methodology; Software, Validation, Writing - Review & Editing, Supervision, Funding acquisition.

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Figure Legends:

Figure 1: MEDEA Atrial Fibrillation study SPIRIT flow diagram: The schedule of enrolment, allocation, interventions and assessments in the AF panel study according to SPIRIT template.

Figure 2: MEDEA Atrial Fibrillation study schematic diagram. The bidirectional MEDena® 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. DDS: Desert Dust Storm, AF: Atrial Fibrillation HRQoL: Health Related Quality of Life, AFEQT: Atrial Fibrillation Effect on QualiTy of Life questionnaire, GPS: Global Positioning System, SMS: Short Messaging Service text message.

Figure 3: MEDEA Atrial Fibrillation study assessments timeline. Timeline of baseline and follow-up assessments in Atrial Fibrillation panel study for the two study years. DDS: Desert Dust Storm, AF: Atrial Fibrillation HRQoL: Health Related Quality of Life, AFEQT: Atrial Fibrillation Effect on QualiTy of Life questionnaire, ICD: Implantable Cardioverter Defibrillator.

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	STUDY PERIOD - MEDEA Atrial Fibrillation study					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	***Month 0 (t0)*** **(1st study year)** **Month 0 (t_0) (2nd study year)** **Month 0 (t_0) (3rd study year)**	**Month 0 (t_0) (1st study year)** **Month 0 (t_0) (2nd study year)** **Month 0 (t_0) (3rd study year)**	***t_1*** ***Baseline*** **Month 1 (t_1) (1st study year)** **Month 1 (t_1) (2nd study year)** **Month 1 (t_1) (3rd study year)**	***t_2*** **Month 2 (t_2) (1st study yr)** **Month 2 (t_2) (2nd study yr)** **Month 2 (t_2) (3rd study yr)**	***t_x*** **Monthly (t_x) (1st study yr)** **Monthly (t_x) (2nd study yr)** **Monthly (t_x) (3rd study yr)**	***t_{x+1}*** ***End of follow-up*** **Last month (t_{x+1}) (1st study yr)** **Last month (t_{x+1}) (2nd study yr)** **Last month (t_{x+1}) (3rd study yr)**
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Training on MEDEA tools & materials		X				
Allocation		X				
INTERVENTIONS:						
Control			←	—	—	→
Outdoor Exposure Reduction			←	—	—	→
Outdoor & Indoor Exposure Reduction			←	—	—	→
ASSESSMENTS:						
Pacemaker ICD Recordings	X		X			X
Monitoring of location and physical activity			←	—	—	→
AFEQT Questionnaire			X	X	X	X
AF Medication Use			X	X	X	X
Unscheduled Visits to Clinician			X	X	X	X

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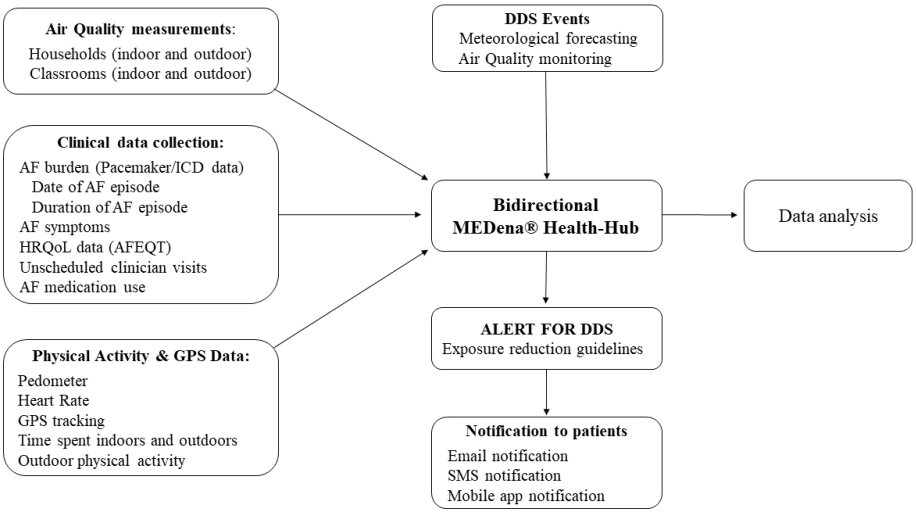

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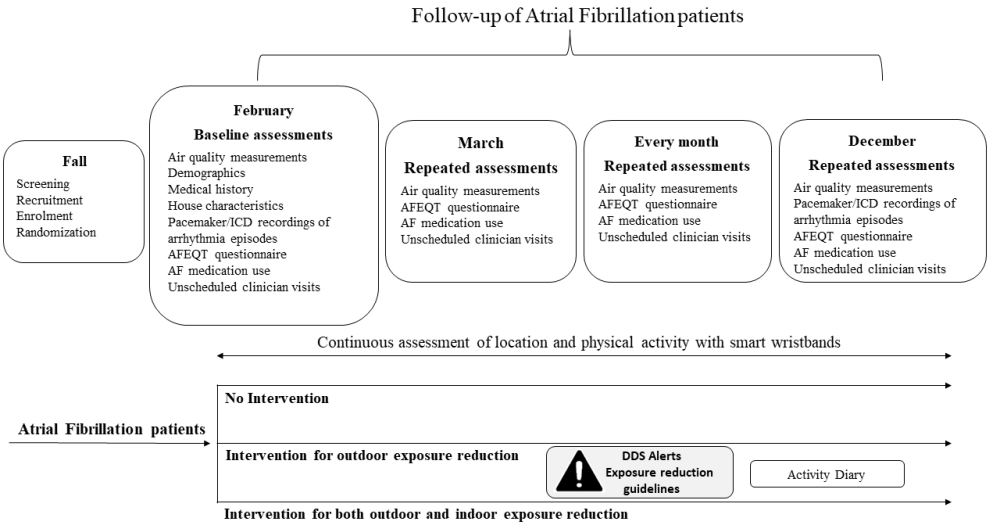

338x190mm (96 x 96 DPI)

SUPPLEMENTARY MATERIAL

Methods and analysis

Details of recruiting AF patients

In order to facilitate recruitment of AF patients, a network of Cardiologists who run large cardiac arrhythmia clinics has been established in collaborating health centers (Nicosia General Hospital, University Hospital of Heraklion and Soroka Research Clinical Center) at each of the three countries. Relations have also been established with the Clinical and Nursing staff of the Clinics and Patients' Associations and the details of the project have been explained to them. Screening of the AF patients at each site started in Summer 2018. The medical/symptom and medication history and downloads from patients' pacemakers or ICDs are obtained and examined in order to assess whether the candidate for enrolment fulfils the eligibility criteria. Patients are able to ask questions for clarification of all aspects of the program. Eligible AF patients are then invited to participate in the MEDEA program after they give written informed consent. An independent researcher provides the sequential number and the assignment group at the baseline clinical visit, who is responsible also for the participants' training on the use of devices after recruitment. Due to the nature of the study, the participants couldn't be blinded to the assignment group.

Details of implementation of the intervention

When predefined algorithms of PM_{10} levels are fulfilled, MEDEA air pollution scientists at each study site, promptly communicate alerts for the appearance of DDS through the e-platform to the participants in the intervention legs of the study, but not to the participants in the control group. To this effect, emails, smartphone applications and text messaging are used to disseminate the specific exposure reduction recommendations in text and animated videos. The participants are familiarised at recruitment with the respective intervention recommendations through animated videos and take home hard-cover flyers printed in a user-friendly layout, to encourage compliance to the intervention.

In participants who are randomized to the combined outdoor and indoor intervention, we also arrange at recruitment to visit their houses within the same week and install air-cleaning devices. Instructions on the use of air cleaners are provided to patients on site. During the home visit, we also assess the placement, and thus functionality of the air cleaner, in a room of the house where the participant spends most of the time (typically between bedroom and sitting room). Reminders are taped on the air cleaners advising to keep them functioning continuously, throughout the six-month study period. Monthly clean-ups of the HEPA filters of the air cleaner are performed by the research staff, as recommended by the manufacturer.

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Study organisation & coordination

DATA ACCESS, OWNERSHIP OF RESULTS, DATA TRANSFER AND PUBLICATION AGREEMENTS

A consortium agreement signed by all participating centers sets the obligations for data access, ownership of results, data transfer and publication agreements.

RESPONSIBILITIES AND COMMITTEES

Coordinating center: Apart from the coordination of the study, the coordinating center is responsible for the acquisition of rights for tools usage.

Data management team: The team consists of researchers form the three centers aiming to ensure data collection, data cleaning and the appropriate preparation of the study dataset.

Steering Committee: The Steering Committee scrutinizes the quality of the project performance, acts as a supervisory body to ensure that the work described in individual actions is carried out and is responsible for troubleshooting. The members of the steering committee include the Project Coordinator, Project Manager, and the Leaders of all other project partners (Soroca Clinical Research Center, University of Crete, Cyprus University of Technology, E.n.A. Consulting, Department of Labor Inspection, Cyprus Broadcasting Corporation, Cyprus Department of Meteorology).

External Advisory Committee: The external advisory committee is responsible to counsel the project and to help transform our results to policies. It consists of 33 members from relevant regulatory authorities and interested stakeholders from all participating sites (Cyprus, Greece, Israel).

A data monitoring committee was not needed for this study, because the participants are adults, the behavioural intervention has very low chance of producing harm, and the duration of the follow-up period for each participant is short (6 months).

PARTICIPANT CONFIDENTIALITY

Administrative safeguards:

Data are completely anonymized and encrypted prior to sending to the central database. The full record of AF participants with names, addresses, and other personal information are kept by the principal investigator (PY) at the Medical School of the University of Cyprus and only authorized personnel will have access to this data (LIFE MEDEA+ project scientist PK). All collected data will be analyzed and discussed between program partners only by using codes (a participant identification number (Participant ID, PID) to ensure that the anonymity of the participants is fully preserved and to maintain confidentiality.

Technical safeguards:

Electronic access to patient data requires a user name and password that is only held by authorized personnel. All computer entry and networking programs are done using PIDs only. In addition, the Microsoft Azure storage platform used for the purpose of data storage and backup, is Health Insurance

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Portability and Accountability Act (HIPAA) compliant that establishes requirements for the use, disclosure, and safeguarding of individually identifiable health information.

The University of Cyprus has a policy that requires computer users not to leave computers unattended and not to exchange entry codes between them. Still, it is worth mentioning that after a few hours of non-use, the computer automatically turns off and locks again, requiring the use of the input code again. In the event that a computer containing personal data is no longer used, the University of Cyprus ensures that the data will either be transferred or destroyed.

Physical safeguards:

The Medical School of the University of Cyprus is housed at the Shakolas Educational Center, a safe building on Nicosia-Limassol Old Road, in Aglantzia, Nicosia. The building is protected internally and with the supervision of the surrounding area, on a daily basis with a 24-hour security guard. The guard checks all incoming people in the building. Data that may be in print will be kept in a closet in the office of the Project Coordinator so that no unauthorized person has access to them. All records will be kept in a locked file cabinet.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	14
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Supplementary material
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

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Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8, 9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10 & Figure 3

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Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6 & supplementary material
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Supplementary material
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Supplementary material
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Supplementary material
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

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Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8 & Supplementary material
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

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Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplementary material
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10-11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

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Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplementary material
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplementary material
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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BMJ Open

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

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Primary Subject Heading:	Occupational and environmental medicine
Secondary Subject Heading:	Cardiovascular medicine, Public health, Health policy
Keywords:	Pacing & electrophysiology < CARDIOLOGY, PUBLIC HEALTH, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical Trial

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Video S2.mov

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Title: The MEDEA randomized 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 (299 words)

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 MEDEA clinical randomised intervention study in adults with AF is funded by EU LIFE+ program 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 randomized 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 GPS 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 (AFEQT) questionnaire.

Ethics and dissemination:

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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, 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.

Registration details: ClinicalTrials.gov Identifier: NCT03503812, April 18, 2019

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.
- Personalized assessment reduces the risk of exposure missclassification
- The study uses validated tools to assess health outcomes, including AF burden and quality of life.
- Advanced age and/or other co-morbidities (e.g. impaired vision) of study participants may compromise the use of wearable devices and smartphones.

Key words: Desert Dust, Asian Dust, Atrial Fibrillation, Public Health Intervention, Sensors

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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 is associated with higher incidence of cardiac infarction [3] and ventricular arrythmias [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 particulate matter (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

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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 "MEDEA (Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches) 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 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 SPIRIT checklist has been used for this report [24].

Population

The target population are 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 (SCRC) in Beer-Sheba, Israel and University Hospital of Heraklion, Crete, Greece. Additional details on the recruitment of participants are provided in Supplementary Material. Screening of the AF patients at each site started in Fall 2018 and MEDEA personnel continues to identify and follow-up eligible AF patients throughout

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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 two months prior to randomization, with:

a. History of paroxysmal AF and

b. 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 (e.g. 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 randomized 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 indoors, and avoid any intense physical activity outdoors, competitive sports and unnecessary walks (Group 2 & Group 3). For indoor exposure reduction intervention, it is recommended to close doors and windows, to seal possible openings around doors and windows minimizing outdoor air penetration, and to filter indoor air by using continuously an air cleaning device (Coway Storm 1516D,

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Coway, South Korea, see Supplementary Material for further details). Indoor exposure reduction measures are implemented at the households of the participants 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, Video S1) and for the outdoor and indoor exposure reduction intervention (Group 3, Video S2) are available in Supplementary Material.

MEDena® Health-Hub

For the purposes of the project, a patient-centered 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 (personalized to each participant, according to the randomization 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 alerts to participants based on increased PM concentrations (including both particles of desert dust and anthropogenic origin) compared to 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, they 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 randomization, participant's socio-demographic 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

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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

i. Wearable sensors: Physical activity as well as time spent outdoors are assessed by the sensors of the EMBRACE™ smartwatch. The smartwatch is supplied with global positioning system (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. Lastly, the software can synchronize the sensors, so that data are transferred to the cloud database marked with the same timestamp.

ii. 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 PM_{10}, $PM_{2.5}$, black carbon (BC) and elements inside and outside representative houses during DDS and DDS-free days.

iii. Questionnaires: Each participant is asked to complete an activity questionnaire following each DDS event, which assesses the reported compliance to the recommendations. A schematic diagram 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

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minimal technical problems with the wearables and devices, as well as to facilitate the compliance of the participants, we maintain an extended support system characterized 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 socio-demographic characteristics, health symptoms, particularly heart arrhythmias symptoms, utilization 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 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 Supplementary Material.

Atrial fibrillation outcomes and data analysis

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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 health-related quality of life, changes equal or greater than (±) 5 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.

i. 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 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.

ii. Statistical analysis plan: Descriptive statistics will be presented using summaries of key variables in the form of mean (standard deviation) 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 Chi-Square 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 previously [30] 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 health-related quality of life (AFEQT score) will rely on a linear mixed

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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 (ΕΕΒΚ ΕΠ 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 center at recruitment. The study has been registered and approved by the clinicaltrials.gov online repository (ClinicalTrials.gov Identifier: NCT03503812)

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 organizations and the general public through publication of a series of short-piece articles for professional websites and newsletters, as well as through the organization of educational activities and open public fairs in the three study sites. Lastly, the LIFE MEDEA project dissemination plan also includes the production of 50-minute documentary with a summary of the study findings that will be made available in English, Greek and Hebrew languages. The anonymised study

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dataset 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.

LIST OF ABREVIATIONS

DDS – Desert Dust Storms

PM_{10} – Particulate Matter <10 μm

$PM_{2.5}$ – Particulate Matter <2.5 μm

AF – Atrial Fibrillation

GPS – Global Positioning system

BC – Black Carbon

ICD – Implantable Cardioverter-Defibrillator

AFEQT – Atrial Fibrillation Effect on Quality of Life

AUTHORS' COMPETING INTERESTS

The authors declare no conflict of interest

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AUTHORS CONTRIBUTIONS

PAnagnostopoulou: Methodology, Data curation, Writing-Original draft preparation, Review & Editing; **PKouis**: Methodology, Investigation, Software, Data curation, Project Administration Writing-Original draft preparation, Review & Editing; **SP**: Conceptualization, Methodology, Data curation, Writing-Original draft preparation; **NM**: Methodology, Writing - Review & Editing; **IP**: Data curation, Investigation, Writing – Review & Editing; **PAvraamides**: Data curation, Investigation, Writing – Review & Editing; **ES**: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing; **IA:** Data curation, Investigation, Writing – Review & Editing; **VN**: Conceptualization, Methodology, Writing - Review & Editing, Project Administration; **GS**: Conceptualization, Data Curation, Software, Visualisation, Writing - Review & Editing; **ER**: Conceptualization, Data Curation, Software, Visualisation, Writing - Review & Editing; **CK**: Visualisation, Resources, Writing - Review & Editing; **FT**: Conceptualization, Methodology, Resources, Software, Writing - Review & Editing; **CS**: Conceptualization, Methodology, Resources, Writing - Review & Editing; **PKoutrakis**: Conceptualization, Methodology; Software, Validation, Resources, Writing - Review & Editing; **PY**: Conceptualization, Methodology; Software, Validation, Writing - Review & Editing, Supervision, Funding acquisition.

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Figure Legends:

Figure 1: MEDEA Atrial Fibrillation study SPIRIT flow diagram: The schedule of enrolment, allocation, interventions and assessments in the AF panel study according to SPIRIT template.

Figure 2: MEDEA Atrial Fibrillation study schematic diagram. The bidirectional MEDena® 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. DDS: Desert Dust Storm, AF: Atrial Fibrillation HRQoL: Health Related Quality of Life, AFEQT: Atrial Fibrillation Effect on QualiTy of Life questionnaire, GPS: Global Positioning System, SMS: Short Messaging Service text message.

Figure 3: MEDEA Atrial Fibrillation study assessments timeline. Timeline of baseline and follow-up assessments in Atrial Fibrillation panel study. DDS: Desert Dust Storm, AF: Atrial Fibrillation HRQoL: Health Related Quality of Life, AFEQT: Atrial Fibrillation Effect on QualiTy of Life questionnaire, ICD: Implantable Cardioverter Defibrillator.

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	STUDY PERIOD - MEDEA Atrial Fibrillation study					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	***Month 0 (t0)*** **(1st study year)** **Month 0 (t_0) (2nd study year)** **Month 0 (t_0) (3rd study year)**	**Month 0 (t_0) (1st study year)** **Month 0 (t_0) (2nd study year)** **Month 0 (t_0) (3rd study year)**	***t_1*** ***Baseline*** **Month 1 (t_1) (1st study year)** **Month 1 (t_1) (2nd study year)** **Month 1 (t_1) (3rd study year)**	***t_2*** **Month 2 (t_2) (1st study yr)** **Month 2 (t_2) (2nd study yr)** **Month 2 (t_2) (3rd study yr)**	***t_x*** **Monthly (t_x) (1st study yr)** **Monthly (t_x) (2nd study yr)** **Monthly (t_x) (3rd study yr)**	***t_{x+1}*** ***End of follow-up*** **Last month (t_{x+1}) (1st study yr)** **Last month (t_{x+1}) (2nd study yr)** **Last month (t_{x+1}) (3rd study yr)**
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Training on MEDEA tools & materials		X				
Allocation		X				
INTERVENTIONS:						
Control			←	—	—	→
Outdoor Exposure Reduction			←	—	—	→
Outdoor & Indoor Exposure Reduction			←	—	—	→
ASSESSMENTS:						
Pacemaker ICD Recordings	X		X			X
Monitoring of location and physical activity			←	—	—	→
AFEQT Questionnaire			X	X	X	X
AF Medication Use			X	X	X	X
Unscheduled Visits to Clinician			X	X	X	X

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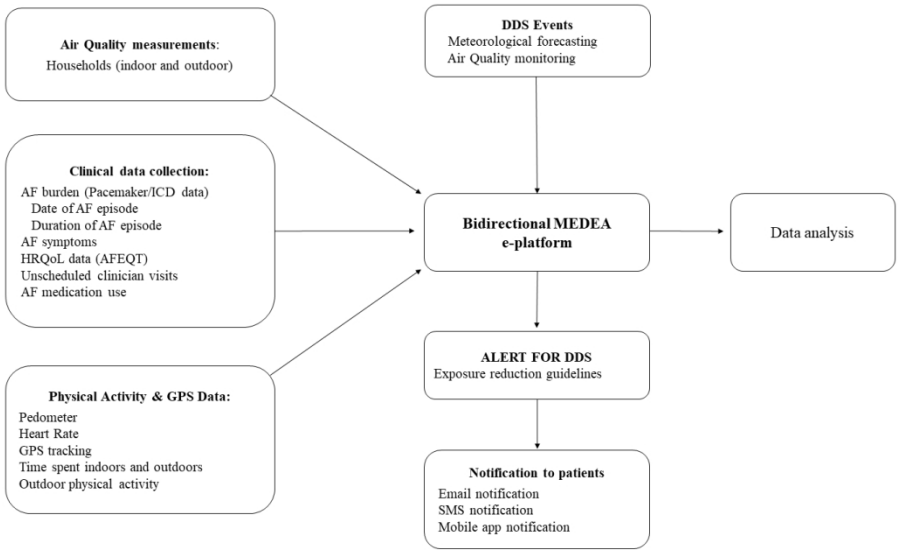

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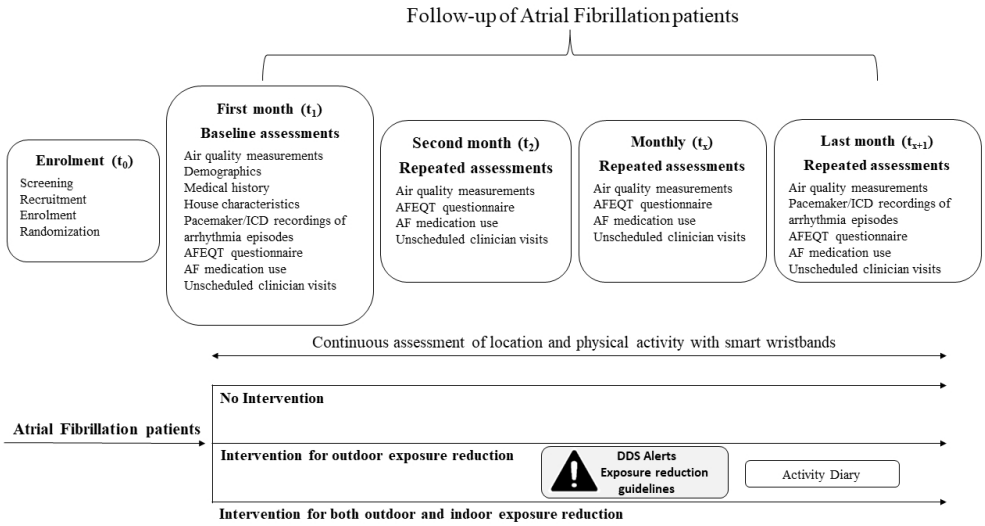

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SUPPLEMENTARY MATERIAL

Methods and analysis

Details of recruiting AF patients

In order to facilitate recruitment of AF patients, a network of Cardiologists who run large cardiac arrhythmia clinics has been established in collaborating health centers (Nicosia General Hospital, University Hospital of Heraklion and Soroka Research Clinical Center) at each of the three countries. Relations have also been established with the Clinical and Nursing staff of the Clinics and Patients' Associations and the details of the project have been explained to them. Screening of the AF patients at each site started in Summer 2018. The medical/symptom and medication history and downloads from patients' pacemakers or ICDs are obtained and examined in order to assess whether the candidate for enrolment fulfils the eligibility criteria. The age itself has not been used as a limiting factor for the participation in the study, but the inability to understand and use study tools (smartphones, software applications), due to age, intellectual disability, etc. Also, patients on terminal illness, bed-bound patients and/or patients with impaired physical mobility are excluded from the study, due to the limited outdoor exposure. The patients' recruitment has been facilitated by the medical staff of cardiology clinics, who are aware of the medical history (e.g. permanent AF, other reversible causes of AF), the comorbidities (e.g. visual impairment, hearing impairment), the lifestyle habits (e.g. active smoking, regular change of household) and the readiness of each patient to participate in the study and comply with the basic requirements.

Patients are able to ask questions for clarification of all aspects of the program. Eligible AF patients are then invited to participate in the MEDEA program after they give written informed consent. An independent researcher provides the sequential number and the assignment group at the baseline clinical visit, who is responsible also for the participants' training on the use of devices after recruitment. Due to the nature of the study, the participants couldn't be blinded to the assignment group.

Several old types of pacemakers implanted to AF patients do not store more than 16 arrhythmia episodes. Thus, for the performance of the AF panel study we rely mainly on patients with implanted ICD's or modern pacemakers such as Advisa (Advisa DR MRI™ and Advisa SR MRI™, Medtronic, United States) and Adapta (Adapta DRTM and Adapta SRTM, Medtronic, United States). These pacemakers save all fast rate episodes, regardless of the time interval between interrogations of the device.

Details on wearable devices

One of the main and earliest challenges of the project was the memory capacity and energy efficiency of the device, as this may affect the credibility of the collected data. In order to overcome this issue, we evaluated several commercially available smart watch devices and we chose the LEMFO-LM25 smartwatch equipped with the EMPBRACETM software (Embrace Tech LTD, Cyprus). This smartwatch does not require manual synchronization with another

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device but acts as a stand-alone device that is able to upload data automatically when it gets in contact with the WI-FI network at the participant's house.

Details of implementation of the intervention

When predefined algorithms of PM_{10} levels are fulfilled, MEDEA air pollution scientists at each study site, promptly communicate alerts for the appearance of DDS through the e-platform to the participants in the intervention legs of the study, but not to the participants in the control group. To this effect, emails, smartphone applications and text messaging are used to disseminate the specific exposure reduction recommendations in text and animated videos. The participants are familiarised at recruitment with the respective intervention recommendations through animated videos and take home hard-cover flyers printed in a user-friendly layout, to encourage compliance to the intervention.

In participants who are randomized to the combined outdoor and indoor intervention, we also arrange at recruitment to visit their houses within the same week and install air-cleaning devices. Instructions on the use of air cleaners are provided to patients on site. During the home visit, we also assess the placement, and thus functionality of the air cleaner, in a room of the house where the participant spends most of the time (typically between bedroom and sitting room). Reminders are taped on the air cleaners advising to keep them functioning continuously, throughout the six-month study period. Monthly clean-ups of the HEPA filters of the air cleaner are performed by the research staff, as recommended by the manufacturer.

Study organisation & coordination

DATA ACCESS, OWNERSHIP OF RESULTS, DATA TRANSFER AND PUBLICATION AGREEMENTS

A consortium agreement signed by all participating centers sets the obligations for data access, ownership of results, data transfer and publication agreements.

RESPONSIBILITIES AND COMMITTEES

Coordinating center: Apart from the coordination of the study, the coordinating center is responsible for the acquisition of rights for tools usage.

Data management team: The team consists of researchers form the three centers aiming to ensure data collection, data cleaning and the appropriate preparation of the study dataset.

Steering Committee: The Steering Committee scrutinizes the quality of the project performance, acts as a supervisory body to ensure that the work described in individual actions is carried out and is responsible for troubleshooting. The members of the steering committee include the Project Coordinator, Project Manager, and the Leaders of all other project partners (Soroca Clinical Research Center, University of Crete, Cyprus University of Technology, E.n.A. Consulting, Department of Labor Inspection, Cyprus Broadcasting Corporation, Cyprus Department of Meteorology).

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External Advisory Committee: The external advisory committee is responsible to counsel the project and to help transform our results to policies. It consists of 33 members from relevant regulatory authorities and interested stakeholders from all participating sites (Cyprus, Greece, Israel).

A data monitoring committee was not needed for this study, because the participants are adults, the behavioural intervention has very low chance of producing harm, and the duration of the follow-up period for each participant is short (6 months).

PARTICIPANT CONFIDENTIALITY

Administrative safeguards:

Data are completely anonymized and encrypted prior to sending to the central database. The full record of AF participants with names, addresses, and other personal information are kept by the principal investigator (PY) at the Medical School of the University of Cyprus and only authorized personnel will have access to this data (LIFE MEDEA+ project scientist PK). All collected data will be analyzed and discussed between program partners only by using codes (a participant identification number (Participant ID, PID) to ensure that the anonymity of the participants is fully preserved and to maintain confidentiality.

Technical safeguards:

Electronic access to patient data requires a user name and password that is only held by authorized personnel. All computer entry and networking programs are done using PIDs only. In addition, the Microsoft Azure storage platform used for the purpose of data storage and backup, is Health Insurance Portability and Accountability Act (HIPAA) compliant that establishes requirements for the use, disclosure, and safeguarding of individually identifiable health information.

The University of Cyprus has a policy that requires computer users not to leave computers unattended and not to exchange entry codes between them. Still, it is worth mentioning that after a few hours of non-use, the computer automatically turns off and locks again, requiring the use of the input code again. In the event that a computer containing personal data is no longer used, the University of Cyprus ensures that the data will either be transferred or destroyed.

Physical safeguards:

The Medical School of the University of Cyprus is housed at the Shakolas Educational Center, a safe building on Nicosia-Limassol Old Road, in Aglantzia, Nicosia. The building is protected internally and with the supervision of the surrounding area, on a daily basis with a 24-hour security guard. The guard checks all incoming people in the building. Data that may be in print will be kept in a closet in the office of the Project Coordinator so that no unauthorized person has access to them. All records will be kept in a locked file cabinet.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	14
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Supplementary material
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

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Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8, 9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10 & Figure 3

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Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6 & supplementary material
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Supplementary material
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Supplementary material
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Supplementary material
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

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Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8 & Supplementary material
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

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Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplementary material
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10-11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

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Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplementary material
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplementary material
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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