Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches (MEDEA) project

ACTION C.8: Assessment of health outcomes in adults with atrial fibrillation during desert dust storm (DDS) events (with vs without intervention measures)

Public Health Intervention Study

Protocol Template

(April 2018)

MITIGATING THE HEALTH EFFECTS OF DESERT DUST STORMS USING EXPOSURE-REDUCTION APPROACHES (MEDEA) PROJECT

ACTION C.8: ASSESSMENT OF HEALTH OUTCOMES IN ADULTS WITH ATRIAL FIBRILLATION (AF) DURING DESERT DUST STORM (DDS) EVENTS (WITH VS WITHOUT INTERVENTION MEASURES)

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Supported by:

LIFE+ 2016

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SUMMARY

Study Title

Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches (LIFE+ MEDEA)

Objectives

The primary objective of this panel study will be to quantify the vulnerability of adults with atrial fibrillation (AF) during desert dust storm (DDS) outbreaks and provide evidence-based estimates demonstrating which intervention/ recommendations work best in mitigating adverse health effects in this group of patients (primary outcome: reduction of atrial fibrillation burden by 20%) after randomization to three parallel intervention groups:

a) no intervention for DDS
b) intervention for outdoor exposure reduction, and
c) interventions for both outdoor and indoor exposure reduction

The secondary objectives of the study are to:

1. Demonstrate which of the recommendations are effective in reducing outdoor and indoor exposures to DDS in a panel of adults with atrial fibrillation (AF)
2. Secondary health outcomes will be the occurrence of ventricular arrhythmias assessed through the pacemaker and heart rate variability.

Design, Interventions and Outcomes

Type of study: Public Health Intervention Study

Intervention: Patients with AF will be recruited and will be randomized during the high DDS outbreaks season (Spring 2019 and 2020) with 1:1:1 ratio into three parallel groups to receive:

a) No intervention for DDS.
b) Intervention for outdoor exposure reduction, by reducing the time spend outdoors and by avoiding physical activity.
c) Interventions for outdoor (as above) and indoor exposure reduction (by minimizing home ventilation and filtering indoor air).

Disease-related adverse health outcomes will be assessed in the three parallel arms of the study.

Approaches for delivering the intervention:

- A bidirectional, patient-centered e-Platform will be developed in order to facilitate prompt communication with the participants and provide early warnings regarding forecasted

upcoming DDS events through text messaging and smartphone applications. Furthermore, the same IT platform and mobile application will be utilised for the dissemination of the exposure reduction guidelines that the participants will follow, depending on which arm of the study they have been randomised to.

Assessment of adherence to intervention:

- Monitor compliance to exposure-reduction guidelines using remote sensors. The intervention for outdoor exposure reduction, entailing reduction of the time spend outdoors and avoidance of physical activity, will be assessed with the use of smart wristwatches that will have a global position system (GPS) and an accelerometer.
- The intervention for indoor exposure reduction, entailing minimization of home ventilation and filtering of indoor air, will be assessed with the use of particle samplers that will be placed outside and inside of houses and school classrooms.

Assessment of health outcomes:

- Daily recordings of AF/ventricular arrhythmia episodes from the participants' pacemakers during the 4-month study period will be downloaded with interrogation of the pacemaker during a visit to the Arrhythmia Clinic after the end of the monitoring period.
- Phone interviews every 1 month throughout the high DDS period recording symptoms of fatigue, change in medication use, and unscheduled visits to health professionals for heart arrhythmias/episodes.
- Continuous recordings of biological parameters (pulse rate, pulse rate variability, temperature) will be obtained by wearing smart watch sensors that will be uploaded on line to e-platform.

Primary health outcome will be every detected high atrial frequency episode of >330 ms (180 beats per minute) lasting for longer than 30 s with an atrial sensitivity of 0.5 mV (assumed as an episode of AF). AF burden is defined as the overall time percentage with AF during the observed period. For the primary analysis, we will compare the combined effect in the two intervention groups versus the control group. Secondarily, the effectiveness of each intervention will be compared versus the control group and to each other.
Secondary health outcomes will be the occurrence of ventricular arrhythmias assessed through the pacemaker and heart rate variability.

Duration

Duration of the study: A feasibility (pilot) trial and refinement of protocols and tools will be performed during the high DDS outbreaks season of 2018. During the fall of 2018 and 2019, MEDEA personnel will initiate the recruitment procedure to enrol eligible AF patients for the two

main study periods (high DDS outbreaks season of February to May 2019 and 2020). Data collection, data cleaning and statistical analysis will take place in 2020.

Study Population

Study population, sample size and location: Men and women with prior implantation of a dual lead (atrial and ventricular) pacemaker or ICD, will be recruited from cardiac arrhythmia clinics in General Hospital in Nicosia-Cyprus (n=156) in project years 2018-2019 and 2019-2020. Recruitment of participants will be facilitated through the network of physicians in Nicosia General Hospital. In order to facilitate recruitment, relations will be established with the Administrative and Nursing staff of the Clinics and Patients' Associations and the details of the project will be explained to them. During fall 2018 and 2019, MEDEA personnel will start recruitment efforts to detect eligible AF patients for participation in the study in the high DDS periods of February-May 2019 and 2020.
The same number of patients will be recruited in each study site (Beer Sheba, Heraklion, Nicosia) and we expect that a total of 468 AF patients will be recruited. We estimate a dropout rate of 30%, which will eventually give us 324 AF patients to analyse. The feasibility of protocols to assess health outcomes in vulnerable patient groups will be tested in the pilot study during the high DDS outbreaks season of 2018 with and without implementation of exposure reduction guidelines in all study sites in a small number of patients (6 AF patients per study site).

1 WORKING HYPOTHESIS

We hypothesize that there will be a reduction of the total AF burden compared to the control group in:

a) The group with intervention aimed to outdoor exposure reduction (b).
b) The group with intervention aimed to outdoor and indoor exposure reduction (c).
c) Both (b) and (c) groups combined as compared to the control.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this panel study will be to quantify the vulnerability of adults with atrial fibrillation (AF) during DDS outbreaks and provide evidence-based estimates demonstrating which intervention/ recommendations work best in mitigating adverse health effects in this group of patients (primary outcome: reduction of atrial fibrillation burden by 20%) after randomization to three parallel intervention groups:

a) no intervention for DDS
b) intervention for outdoor exposure reduction, and
c) interventions for both outdoor and indoor exposure reduction

The primary health outcome will be defined by using every detected high atrial frequency episode of >330 ms (180 beats per minute) lasting for longer than 30 s with an atrial sensitivity of 0.5 mV (assumed as an episode of AF). AF burden is defined as the overall time percentage with AF during the observed period. For the primary analysis, we will compare the combined effect in the two intervention groups versus the control group. Secondarily, the effectiveness of each intervention will be compared versus the control group and to each other.

2.2 Secondary Objectives

The secondary objectives of the study are to:

1. Demonstrate which of the recommendations are effective in reducing outdoor and indoor exposures to DDS in a panel of adults with atrial fibrillation (AF)
2. Secondary health outcomes will be the occurrence of ventricular arrhythmias assessed through the pacemaker and heart rate variability.

3 BACKGROUND AND RATIONALE

3.1 Background on Condition, Disease, or Other Primary Study Focus

The MEDEA project is envisioned to provide the field-based evidence for the adoption of a strategic plan for mitigating the health effects of desert dust storm (DDS) events in South-Eastern Europe. Over the past decade, several studies have demonstrated that DDS in Mediterranean countries, originating mostly from the Sahara and Arabian Peninsula deserts, have been increasing in number and magnitude and linked it to desertification, climatic variability and global warming. EU legislation considers DDS impossible to prevent, implicitly harmless and discounts their contribution to daily and annual air quality standards of particulate matter up to 10 microns (PM10).

However, there is increasing evidence from epidemiological studies which correlates exposure to PM10 during DDS with a significant increase in mortality and hospital admissions from cardiovascular and respiratory causes. Therefore, there is a pressing need for EU policies to reduce population exposures and increase individual, population and institutional resilience to the growing frequency and intensity of DDS.

MEDEA ultimate goal is to demonstrate the feasibility and effectiveness of an adaptation strategy to DDS and better inform EU policy making.

3.2 Study Rationale

Desert dust storm events across Southern Europe

A dust storm is a phenomenon common to arid and semi-arid regions. In the EU, the term "Desert Dust Storms (DDS)" is used in the context of sandstorms originating primarily from the Sahara desert but also from the Arabian–Negev desert. The term DDS refers to the condition created when finer sand particulate matter (PM) from the desert surface is transported over a long distance. DDS pose a major risk to populations residing in affected areas, such as in Mediterranean countries belonging to the global dust belt, extending from West Africa to the Arabian Peninsula (Querol et al., 2009). During DDS events, which can last for several days, PM_{10} levels are considerably higher than the 2005 EU daily limit value of 50 $\mu g/m^3$ (Achilleos et al, 2014). Dust PM is mostly composed of rock-forming and clay minerals and they may carry microbial agents, such as bacteria, fungi and viruses (Griffin et al, 2007), and mix with anthropogenic atmospheric pollutants during transport.

Associations of DDS with mortality and hospital admissions

Historically, DDS were not considered harmful to humans due to their natural origin and crustal composition; however, in recent years, a large number of studies worldwide and in particular from Cyprus (Middleton et al., 2008; Neophytou et al., 2013), Greece (Samoli et al., 2011), Italy (Mallone et al., 2011) and Israel (Vodonos et al., 2014) have reported associations of PM_{10} during DDS outbreaks with increased hospital admissions for asthma, chronic obstructive pulmonary disease, cardiovascular disease and increased mortality. The pathogenic effect of PM_{10} inhalation has been attributed to direct physical and toxic action of particles on human airway epithelium and systemic inflammatory responses triggering endothelial dysfunction or dysfunction of the autonomic nervous system (Leski et al., 2011). Increased hospital admissions and mortality are only two of a much larger number of adverse outcomes of exposure to DDS PM_{10}. Beyond these serious complications, patients suffer symptomatic exacerbations of pre-existing conditions, require unscheduled hospital visits, use excessive medications, and lose their sense of well-being, often with days off work or school. These relatively less studied consequences are more common, but largely un-quantified and un-investigated. Finally, DDS PM_{10} exposure is associated with sub clinical effects on the general population, from mild discomfort, eye and skin irritation to substantial effects on biological processes and quality of life.

Framework for designing, implementing and testing an adaptability strategy

Our knowledge of the health risks associated with exposures to DDS PM in southern Europe comes mostly from small-scale local or national studies. Despite their limited scope, these investigations have provided sufficient evidence of a real human health risk affecting a large proportion of the EU population. Reversing the unfavourable climate trends that are exacerbating the effect of DDS in the region is a daunting task, and the benefits of global climate change policies will take decades to realize.

At the moment, the EU national competent authorities and mass media in the DDS-exposed regions, during some of the events, issue not-standardised recommendations to the public/vulnerable groups, most commonly advising them to stay indoors, and reduce outdoor activities. To date, no scientific evidence exists on the effectiveness of any of these recommendations in either reducing the exposure to DDS PM or mitigating related health effects. The EU needs to develop evidence-based policies that increase individual, population, and institutional resilience to the growing frequency and intensity of DDS. We propose in three of the most heavily DDS-affected Mediterranean regions (Cyprus, Crete, and Israel) to apply, test and demonstrate the efficacy of patient-specific and population-wide public health interventions to reduce personal exposures to DDS as a means of adaptation.

This study will address a significant knowledge gap in the health effects of personal exposures to desert dust particles, and establish vulnerability assessments in groups such as adults with AF, driven by our findings on the impact of the interventions on exposure, measures of health, and morbidity, thus enabling participant countries to build adaptation strategies and evidence-based policies. During and after the end of the project, this information and knowledge will be used to fine-tune tools for informed decision-making and strategic planning both at national (individual country stakeholders) and cross national levels and will be disseminated to facilitate an exchange of best practices and raise awareness within the population on their vulnerability to DDS pollutants as set out in EU policy priorities.

4 STUDY DESIGN

Type of study: Randomized clinical trial (Behavioural Intervention)

Patients with AF will be recruited during DDS outbreaks and will be randomized into three parallel groups to receive:

a) No intervention for DDS,
b) Intervention for outdoor exposure reduction, and
c) Interventions for both outdoor and indoor exposure reduction.

Disease-related adverse health outcomes will be assessed in all the parallel arms of the study.

Previous publications of the MEDEA partners (Achilleos et al, 2014; Gerasopoulos et al, 2006; Krasnov et al, 2014), indicated that 2/3 of each year's DDS events in the Eastern Mediterranean region appear during February-May, with 10-15% of the days during this period being "DDS days". Thus we will perform this public health intervention study during February–May of 2019 and 2020.

Study population and location: Men and women with prior implantation of a dual lead (atrial and ventricular) pacemaker or ICD, will be recruited from the cardiac arrhythmia clinic at the Nicosia General Hospital of Cyprus (n=156) in project years 2018-2019 and 2019-2020. Each patient will have assessment of health outcomes during only one high DDS period.

Duration of the study: A feasibility trial and refinement of protocols and tools will be performed in the high DDS period of 2018. In the fall of 2018 and 2019, MEDEA personnel will start recruitment efforts to detect eligible AF patients for participation in the study during the high DDS periods of February-May 2019 and 2020.

Assessment of health outcomes:

- The occurrence of AF/ventricular arrhythmia episodes will be recorded daily using the already implanted participants' pacemakers or ICD during the 4-month study period. The recorded episodes will be downloaded with interrogation of the pacemaker or ICD during a visit to the Arrhythmia Clinic after the end of the study period.
- Phone interviews every 1 month throughout the high DDS outbreaks season will be carried out. Data collected will include symptoms of fatigue, change in medication use and unscheduled visits to health professionals for heart arrhythmias/episodes.
- Continuous recordings of biological parameters (pulse rate, pulse rate variability and temperature) obtained by wearing smart watch sensors and uploaded on line to the secure e-platform.

5 SELECTION AND ENROLLMENT OF PARTICIPANTS

5.1 Inclusion Criteria

The inclusion criteria for this panel study will be patients with permanent dual lead (atrial and ventricular) pacemaker or ICD implanted at least two months prior to randomization, with:

- A history of AF or
- Detection of AF in pacemaker/ICD monitoring (continuous recording)

5.2 Exclusion Criteria

Exclusion criteria will be:

- Permanent AF

- Patients with reversible causes of AF (eg hyperthyroidism)
- Inability to understand and use study tools (smartphones, software applications)
- Terminal illness
- Active smoking
- Not living at least 5 days per week in the household

5.3 Study Enrollment Procedures

Men and women with prior implantation of a dual lead (atrial and ventricular) pacemaker or ICD, will be recruited from the cardiac arrhythmia clinic at Nicosia General Hospital in Cyprus (n=156) in project years 2018-2019 and 2019-2020. Recruitment of participants will be facilitated through the network of physicians at Nicosia General Hospital. In order to facilitate recruitment, relations will be established with the Administrative and Nursing staff of the Clinic and Patients' Association and the details of the project will be explained to them. Patients will be able to ask questions and ask for clarification on all aspects of the program. Each patient participating in the program should complete the necessary consent forms (EKBK03 consent form, see Appendices).

6 STUDY INTERVENTIONS

6.1 Interventions, Administration, and Duration

Following recruitment, we will randomize participants with a 1:1:1 ratio to three parallel groups to receive:

a) no intervention for DDS

b) intervention for outdoor exposure reduction, by reducing the time spend outdoors and by avoiding physical activity

c) interventions for outdoor (as above) and indoor exposure reduction (by minimizing home ventilation and filtering indoor air).

In the indoor intervention arm of the study, exposure reduction measures will be applied in the patient's household/bedroom settings.

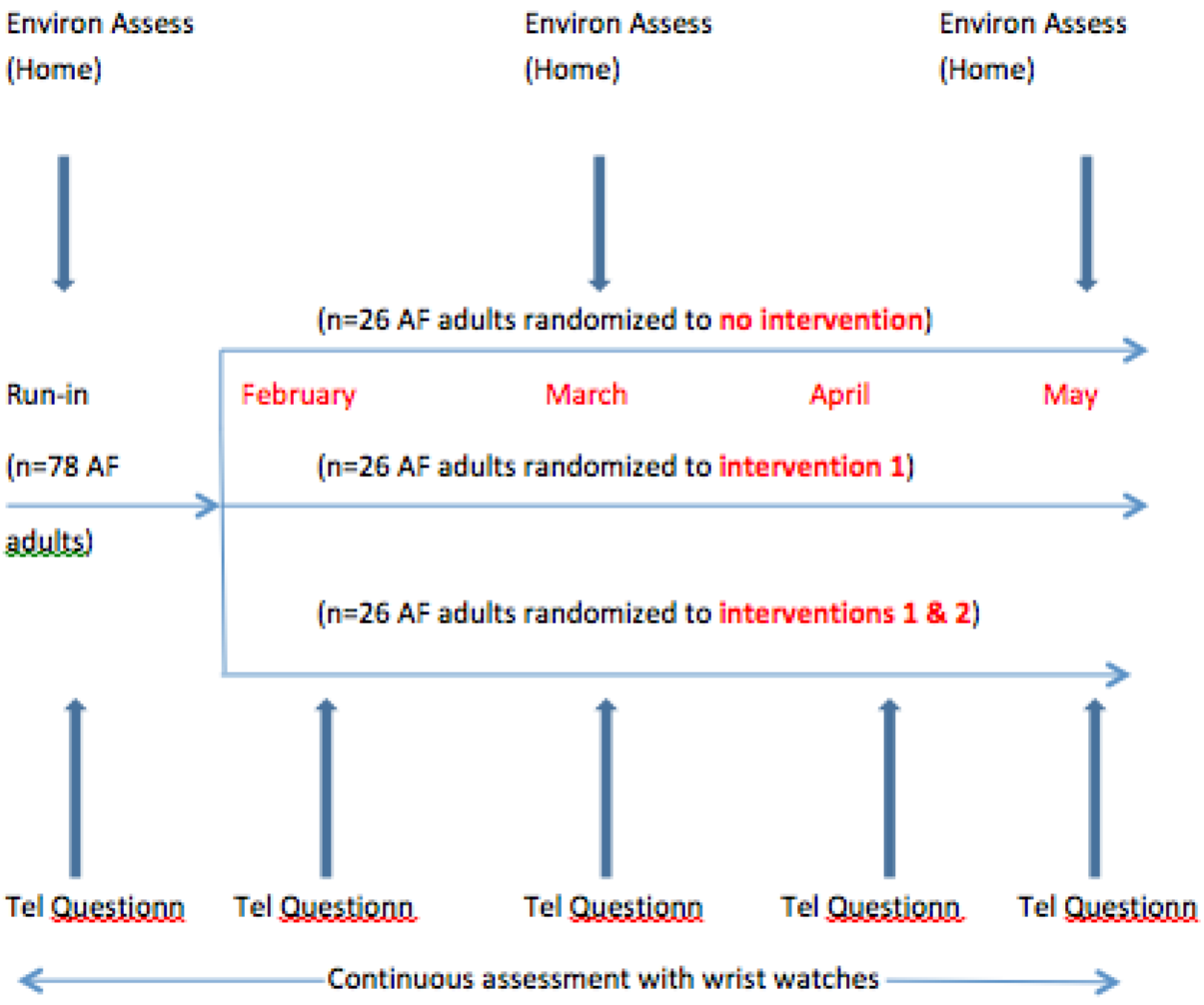
After randomization, and prior to the high DDS season, each eligible participant will complete a questionnaire, providing socio-demographic characteristics, detailed medical and medication history, and will be trained in the tools and procedures to be followed during the monitoring sessions while in the community.

The study design offers also the opportunity to assess:

- outdoor exposures to PM,
- indoor exposures to PM and
- related health outcomes in three parallel groups during the same DDS events with and without intervention measures (Figure C8.1).

Figure C8.1. Study Year 1 (February-May 2019) - 78 patients with AFIB in each study site (Beer Sheba-Israel, Nicosia-Cyprus & Heraklion-Crete) to be randomized to three levels of intervention

(to be repeated in Study Year 2, February-May 2020)



6.2 Handling of Study Interventions

A bidirectional, patient-centered e-Platform will be created to:

- Communicate promptly forecast alerts to individuals about upcoming DDS events through smartphone applications and text messaging
- Disseminate exposure reduction guidelines

In particular, in the group where there will be intervention for outdoor exposure reduction, the intervention will be carried out by:

- Informing the participant for upcoming desert dust storm episodes.
- Simultaneous transmission of instructions to patient's smartphone to reduce outdoor exposure during the episode (stay indoors, avoid intense physical activity outdoors, avoid competitive sports, avoid unnecessary walks).

In the group where there will be interventions for outdoor and indoor exposure reduction, the intervention will be carried out by:

- Informing the participant for upcoming desert dust storm episodes.
- Simultaneous transmission of instructions to patient's smartphone to reduce a) outdoor exposure during the episode (stay indoors, avoid intense physical activity outdoors, avoid competitive sports, avoid unnecessary walks), and b) indoor, home exposure (closed windows and doors, sealing possible cracks around windows and doors in order to minimize home ventilation, and using an air cleaner in order to filter indoor air).

6.3 Adherence Assessment

The compliance to exposure-reduction guidelines will be monitored with the use of remote sensors. The intervention for outdoor exposure reduction, (by reducing the time spend outdoors and by avoiding physical activity) will be assessed with the use of smart wristwatches that will have global position system (GPS) and accelerometer. The intervention for indoor exposure reduction (by minimizing home ventilation and by filtering indoor air) will be assessed with the use of particle samplers that will be placed outside and inside houses.

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7 STUDY PROCEDURES

7.1 Schedule of Evaluations

Assessment	Baseline	Every 1 month ± 3 days.	4 months ± 30 days
Informed Consent Form	X		
Inclusion/Exclusion Criteria	X		
Demographics	X	X	
Medical History	X	X	
House assessment		X	
Current Medications	X	X	X
Intervention Discontinuation		X	X
Tel Questionnaire		X	
Daily recordings of AF/ventricular arrhythmia episodes			X
Continuous recordings of biological parameters (pulse rate, pulse rate variability, temperature)		X	X
Adverse Events		X	X

7.2 Description of Evaluations

7.2.1 Screening and Enrollment Evaluation

These evaluations occur to determine if the candidate is eligible for the study.

Consenting Procedure

Before any screening procedure is performed, informed consent must be obtained. There will be one consenting process that describes the study procedure.
Patients will be asked by the study personnel to read their consent forms, and will be given the opportunity to ask any clarification question for the purposes of the study and their participation. Following a discussion with the patients, they will be asked to give their signed approval. The explanations given to the patients will be in comprehensible non-technical terminology.

Screening and Enrollment

In fall 2018 and 2019, screening of patients attending the cardiac arrhythmia clinic will be performed with the help of the network of physicians at Nicosia General Hospital. During screening, each patient will have at the clinic demographic, medical, medication and symptom survey. The enrollment date is the day the participant has met all the screening criteria (both inclusion and exclusion criteria) and signs the informed consent form.

7.2.2 Baseline Assessment and Randomization

Baseline Assessments

For participants who have successfully been screened for eligibility and are enrolled into the study, baseline assessments will be performed during February of each study year. Prior to the high DDS season, each eligible patient will:

a) Answer a questionnaire regarding socio-demographic characteristics

b) Provide detailed medical and medication history

c) Household characteristics assessment

Randomization

Following the eligibility assessment, participants will be randomized using PASS 14 software that allows for random number generation. Randomization will be carried out with a 1:1:1 ratio to three parallel groups:

a) Control group A: No intervention for DDS,
b) Intervention group B: Intervention for outdoor exposure reduction, and
c) Intervention group C: Intervention for outdoor and indoor exposure reduction (patient's household/bedroom settings)

7.2.3 Follow-up Assessments

- Intervention mid-point assessment April 2019/2020:
  - Current medications
  - Intervention discontinuation
  - Telephone questionnaire
  - Daily recordings of AF/ventricular arrhythmia episodes
  - Continuous recordings of biological parameters (pulse rate, pulse rate variability, temperature)
  - Adverse events

7.2.4 Completion/Final Evaluation

- Intervention end-point assessment May 2019/2020:
  - Current medications
  - Intervention discontinuation
  - Telephone questionnaire
  - Daily recordings of AF/ventricular arrhythmia episodes
  - Continuous recordings of biological parameters (pulse rate, pulse rate variability, temperature)
  - Adverse events

8 STATISTICAL CONSIDERATION AND ANALYSIS PLAN

We will build a spatial-temporal individual-based database to continuously collect air quality and meteorological information along with the patient's heart rate assessments. This unique database will enable a valid analysis of an impact of DDS on heart rate variation.

8.1 Sample size consideration

There are no studies that evaluated the reduction in AF burden attributed to reduction in exposure to ambient air pollution.

We assume that the mean AF burden in the control group will be 15%+/-15%. We conservatively estimated the expected intervention effect to be 20% of relative reduction in AF burden. This is translated into the reduction of AF burden by mean of 43 minutes per 24 hours.

Group sample sizes of 108 and 216 achieve 81% power to show a difference in means when there is a difference of -3.0 between the null hypothesis mean difference of 0.0 and the actual mean difference of 3.0 at the 0.05 significance level (alpha) using a two-sided Mann-Whitney-Wilcoxon Test. These results are based on 2000 Monte Carlo samples from the null distributions: WeibullMS(15 15) and WeibullMS(15 15), and the alternative distributions: WeibullMS(15 15) and WeibullMS(12 15).

8.2 Statistical analysis

8.2.1 Descriptive statistics

Summaries of main variables will be presented in form of means and standard deviations for normal distributed quantitative variables, medians and ranges for non-normal distributed quantitative variables, distribution in percentages for qualitative variables.

8.2.2 Univariate analysis

Univariate analysis will be mostly used for analysis initial datasets consisted of personal data records.

The method of analyses for continuous variables will be parametric using Paired and Unpaired t-test and Repeated Measurements ANOVA.

Non-parametric procedures will be used if parametric assumptions could not be satisfied, even after data transformation attempts. These tests will include Mann-Whitney, Wilcoxon and Spearman Correlation tests.

Categorical variables will be tested using Chi-Square test.

8.2.3 Multivariate analysis

We will apply 2 modelling strategies:

Case- Crossover design

The association between DDS events and episodes of cardiac arrhythmia will be assessed in a case-crossover design [(10)]. This method has been used previously to study triggers of acute cardiovascular events [(11)]. We will define case periods by the time of each confirmed episode of cardiac arrhythmia, rounded to the nearest hour. We will match control periods on weekday and hour of the day within the same calendar month. Conditional logistic regression analysis will be performed to analyze the exposure odds ratio with 95% confidence intervals on risk of cardiac arrhythmia.

Hierarchical model

Generalized Linear Model will be used to fit a Poisson regression of daily AF episodes against temporal variables and DDS data based in hierarchical model. Data model with random effect include repeated episodes of AF in each patien, the intervention groups and the 3 sites of the research. Date model with fixed effect include DDS event during the period of the study.

Analysis will be performed using R Project for Statistical Computing version 3.0 or higher and IBM SPSS software version 23 or higher.

9 ASSESSMENTS OF ADVERSE EVENTS

Since, the intervention under study is behavioral/lifestyle intervention, it does not involve any specific drug administration nor any change in ongoing medication schedule. Furthermore, it does not include any invasive procedure and all the health outcomes are assessed using non-invasive methods (smart-watches, phone interviews) and questionnaires. Hence, there are no specific safety parameters to quantify adverse health events related to interventions.

At any point during the study, patients will have the opportunity to bring any evolving information or issue (e.g. health issue) that concerns them to the attention of the primary investigator, Dr Panayiotis Yiallouros, whose contact information will be given to all

participants during the enrollment phase, and will also be available on the program's website.

10 INTERVENTION DISCONTINUATION

Subjects may withdraw voluntarily from the study at any time and for any reason.

Patients can make oral complaints to members of the research team as well as to the principal investigators of each site.

The criteria for intervention discontinuation will be:

- Non-adherence to the intervention
- Moving to a different house than the reported initial one
- Significant change in health status

11 DATA COLLECTION

11.1 Data Collection Forms

Health assessment data:

- The baseline demographic (gender, age, city), medical, medication and symptom data will be obtained using surveys/questionnaires.
- Daily recordings of AF/ventricular arrhythmia episodes will be obtained from the participants' pacemakers.
- Symptoms of fatigue, change in medication use, and unscheduled visits to health professionals for heart arrhythmias/episodes will be recorded via phone interviews.
- Continuous recordings of biological parameters (pulse rate, pulse rate variability, temperature) obtained by wearing smart watch sensors.

Exposure data:

- Household characteristics will be assessed with the help of a questionnaire at the onset of the study.
- Real time location data will be assessed using personal smartphones application for The Global Positioning System (GPS), satellite-based navigation system installed in every smartphone.
- Real time location data from the GPS will be coupled with accelerometer data from smart wristwatches.
- Hourly central data on air pollutants, including; ambient concentrations of PM_{10}, $PM_{2.5}$, as well as meteorological factors (temperature and relative humidity).

- Outdoor and indoor PM and chemicals at participants' households.

11.2 Data Management

The study will be overseen and managed by the Medical School, University of Cyprus, under the supervision of the LIFE+ MEDEA principal investigator, Professor Panayiotis Yiallouros.
All collected data, will be analyzed and discussed between LIFE+ MEDEA partners only by using codes to ensure that the anonymity of the participants is fully preserved.

12 PARTICIPANT RIGHTS AND CONFIDENTIALITY

Patients will be informed about the program and the data to be obtained through the information material that will provided with the consent form.

During the study, patients will have the opportunity to get any additional information on any subject that concerns them from the study personnel and or principal investigator (project coordinator) Professor Panayiotis Yiallouros whose contact information will be given to all participants during the recruitment process and will also be available on the program's website.

Also, any relevant conclusions resulting from the collected data analysis will be communicated to patients at the end of the program. This information will concern the better monitoring and forecasting of dust storms and the results of the interventions in order to reduce exposure of the population to DDS events.

12.1 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record.

12.2 Participant Confidentiality

Administrative safeguards:
Data will be completely anonymized and encrypted prior to sending to the central database. The full record of Cypriot AF patients with names, addresses, and other personal information will be kept by the principal investigator, Professor Panayiotis

Yiallouros at the Medical School of the University of Cyprus and only authorized personnel will have access to this data (LIFE MEDEA+ project scientist Panayiotis Kouis). All data to be collected, 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 Cypriot patient data will require a user name and password that will only be held by authorized personnel. All computer entry and networking programs will be done using PIDs only. In addition, the Microsoft Azure storage platform that will be 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 will ensure that the data will either be transferred or destroyed.

Physical safeguards:
The Medical School of the University of Cyprus is housed at the Shiakolio 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.

13 ETHICAL CONSIDERATIONS

The study has already obtained clearance from the Cyprus National Bioethics Committee. The intervention under study meets the criteria of the Helsinki declaration and follows the ICH/GCP and EC rules of good clinical practice. Data from individual countries will be completely anonymized and encrypted prior to sending to the central database.

There are no significant ethical considerations, since all necessary safeguards will be taken so that all participants do not face any risk and their personal data is protected. Participation

will be on a voluntary basis and all participants will be able to withdraw at any point in the program.

14 COMMITTEES

Steering Committee:

The Steering Committee will scrutinize the quality of the project performance and will act as a supervisory body to ensure that the work described in individual actions is carried out. The members of the steering committee will 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). The Steering Committees will be responsible for the:

- Decisions on technical roadmaps for the project and monitoring implementation;
- Provision of data for preparation of reports and deliverables to the Commission.

External Advisory Committee:

The external advisory committee will be responsible to counsel the project and to help transform our results to policies. The advisory committee will consist of relevant regulatory authorities and interested stakeholders. There will be in total 30 members from all participating sites (Cyprus, Greece, Israel, i.e. ~10 members from each site).

15 REFERENCES

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16 SUPPLEMENTS/APPENDICES

I. Informed Consent Form Template