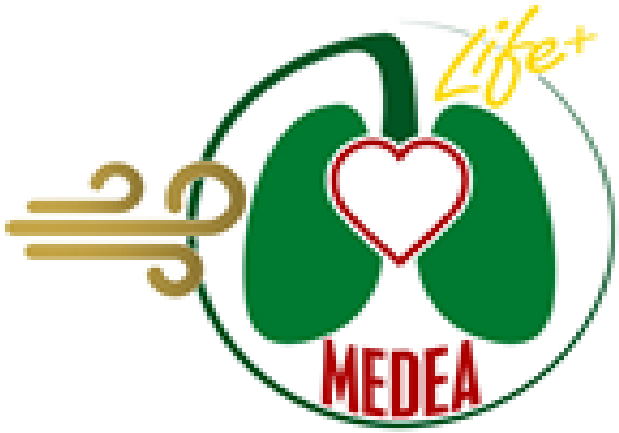
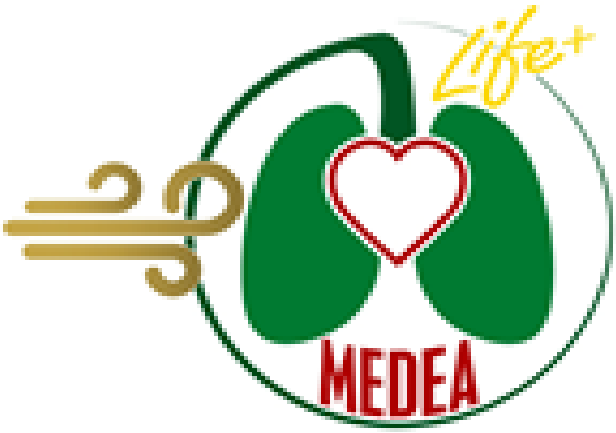


Sub-Action C.1

Deliverable C1.5. Protocols for assessment of health outcomes in vulnerable patient groups (AF cohort, children with asthma) and preliminary health data from the pilot studies

Responsible beneficiary: UCY

Date: 31/08/2018



Sub-action C.1.5.

Deliverable C1.5: Protocols for assessment of health outcomes in vulnerable patient groups (AF cohort, children with asthma) and preliminary health data from the pilot studies.

Responsible beneficiary: UCY

Date: 31/08/2018

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Introduction

The deliverable "Protocols for assessment of health outcomes in vulnerable patient groups (AF cohort, children with asthma) and preliminary health data from the pilot studies" is part of Action C.1.5 ("Development and testing of protocols for recruitment and assessment of health outcomes in vulnerable patient groups with Atrial Fibrillation – AF cohort and children with asthma").

At the moment during DDS episodes, the EU national competent authorities and mass media in the DDS-exposed regions on some of the events, issue non-standardized recommendations for citizens to stay indoors and reduce outdoor activities. To date no scientific evidence exists on the effectiveness of any of these recommendations. In the MEDEA project, a set of simple, easy to implement, cost-effective actions will be adopted by the vulnerable patient participants to reduce outdoor exposure and in a more integrated approach, also indoor exposure, based on the existing scientific evidence. Implementation of these measures during DDS will result in measurable and significant reductions in PM exposures and the associated adverse health effects. The effectiveness of the guidelines in reducing adverse health effects will be evaluated in asthmatic children by symptom diaries/lung function tests and in heart arrhythmia patients will be evaluated by previously implanted pacemakers and by wearable remote sensors, measuring cardiac rhythm and blood pressure.

The aim of Action C.1.5 of the MEDEA project is to develop the protocol for assessment of health outcomes in the study subjects (asthmatic children and atrial fibrillation patients). The protocol for both groups of patients has already been registered at the ClinicalTrials.gov, with the ClinicalTrials.gov Identifier: NCT03503812 (https://clinicaltrials.gov/ct2/show/NCT0350381). Moreover, in the pilot study of the asthmatic children, 12 asthmatic children have been identified eligible for the study and their baseline demographic, anthropometric, medical, and symptom data have been obtained during Spring 2018.

The current report provides in detail the protocol for the assessment of health outcomes in children with asthma and in adults with atrial fibrillation.

Assessment of Health Outcomes in Children with Asthma

Children with asthma 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, 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 asthmatic child's classroom/school and bedroom/household settings.

After randomization, the children, their parents and schoolteachers will be trained in the tools and procedures to be followed.

Prior to the high DDS season, each eligible child will have at the school:

- Baseline demographic, medical, and symptom survey, and
- Assessments of lung function (Spirometry), fractional exhaled nitric oxide (FeNO), and specific aero-allergen sensitivities.

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.

Assessment of health outcomes:

- Phone interviews at baseline and then at every 1 month throughout the high DDS period will be carried out, recording information on asthma medication use and unscheduled visits to health professionals for asthma.
- Frequency of respiratory symptoms will be assessed via caregiver and child's responses to questions on daytime and night-time symptoms in the past 4 weeks, with the help of a validated Greek version of the ACT.
- Lung function, FeNO and specific aeroallergen sensitivities will be assessed at baseline, middle and end of high DDS season

Primary health outcome will be a change of 3 points in the ACT questionnaire score. For the primary analysis we will compare the combined effect in the two intervention groups versus the control group. Next, we will compare between each of the intervention groups and control group and between the intervention groups.
Secondary health outcomes will be the presence or absence of asthma symptoms in the prior 4-week period, asthma medication use, unscheduled visits for asthma, forced expiratory volume in 1 second, peak expiratory flow, and FeNO.

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 be equipped with Global Positioning 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 of houses and school classrooms.

STUDY PROCEDURES

Schedule of Evaluations

Assessment	Screening and Enrollment	Baseline Assessment, and Randomization March 2019/2020	Intervention mid-point assessment April 2019/2020	Intervention end-point assessment May 2019/2020
Informed Consent Form	X			
Demographics	X	X		
Medical History	X	X		
House Assessment		X		
Current Medications	X	X	X	X
Intervention Discontinuation		X	X	X
Tel ACT Questionnaire		X	X	X
Lung function assessment		X	X	X
FeNO assessment		X	X	X
Specific aero-allergen sensitivities assessment		X		
Adverse Events		X	X	X

Description of Evaluations

These evaluations will be performed 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 two consenting processes, one regarding the participation to the screening process and the final one which will regard full study enrollment.

The survey consent form that describes the screening procedure will be given by classroom's teachers to the children to take to their parents at home, whereas the second consent form for enrollment to the study will be handed by the study personnel to children's parents directly.

With the use of screening questionnaires (GAN questionnaires), parents upon written consent will report their child's respiratory health data. Then parents of children with asthmatic symptoms will be invited to participate in the MEDEA program after they have given their written consent. Parents will be asked by the study personnel to read the consent form carefully and will be given the opportunity to ask clarification questions regarding the study and their child's participation. Following a discussion with the parents, they will be asked to give their signed approval. The explanations given to the children will be in comprehensible non-technical terminology.

Screening and Enrollment

The screening procedure with the use of GAN questionnaires, will take place during fall 2018 and 2019. The GAN questionnaire will allow for the collection of demographic, medical, medication and symptom data. The enrollment date is day the child participant has met all the screening criteria (both inclusion and exclusion criteria) and the parent signs the second informed consent form.

Baseline Assessments

Participants who have been successfully screened for eligibility and are enrolled into the study, baseline assessments will be performed during January-February of each study year. Prior to the high DDS season, each eligible child at school will:

a) Answer a questionnaire regarding socio-demographic characteristics
b) Provide detailed medical and medication history (frequency of respiratory symptoms will be assessed via caregiver and child's responses to questions on daytime and nighttime

symptoms in the past 4 weeks, with the help of a validated Greek version of ACT, asthma medication use, unscheduled visits to health professionals for asthma)

c) Have household characteristics assessments

d) Have assessments of lung function (Spirometry), fractional exhaled nitric oxide (FeNO), and specific aero-allergen sensitivities.

Randomization

Following the eligibility assessment and prior to the baseline visit, participating schools (and their students with asthma) will be randomized using standard computer software (Microsoft Excel) 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: Interventions for outdoor and indoor exposure reduction (asthmatic child's classroom/school and household/bedroom settings).

Follow-up Assessments

- Intervention mid-point assessment April 2019/2020:
  - Current medications
  - Intervention discontinuation
  - Telephone ACT questionnaire (monthly)
  - Lung function assessment
  - FeNO assessment
  - Specific aero-allergen sensitivities
  - Adverse events

Completion/Final Evaluation

- Intervention end-point assessment May 2019/2020:
  - Current medications
  - Intervention discontinuation
  - Telephone ACT questionnaire (monthly)
  - Lung function assessment
  - FeNO assessment
  - Specific aero-allergen sensitivities
  - Adverse events

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 regimen. 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 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.

Intervention Discontinuation

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

Parents or guardians of asthmatic children can make oral complaints to members of the research team as well as to the principal investigators of each site.

The criteria for discontinuation of intervention will be:

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

Data Collection Forms

Health assessment data:

- The baseline demographic (gender, age, city), medical, medication and symptom data will be obtained using surveys/questionnaires (GAN).
- The lung function will be assessed using portable spirometers.
- The fractional exhaled nitric oxide (FeNO) will be assessed using handheld fractional exhaled nitric oxide analyzers (NIOX VERO).
- Specific aero-allergen sensitivities will be assessed with skin prick testing.
- Frequency of respiratory symptoms will be assessed via caregiver and child’s responses to questions on daytime and nighttime symptoms in the past 4 weeks, with the help of a validated Greek version of the ACT.

- Information will also be obtained on asthma medication use and unscheduled visits to health professionals for asthma via phone interviews.

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 and school will be assessed with outdoor and indoor samplers.

Assessment of Health Outcomes in Adults with Atrial Fibrillation

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 by reducing the time spend outdoors and by avoiding physical activity, and
c) Interventions for both 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.

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.

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.

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.

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

Description of Evaluations

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.

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)

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

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

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.

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

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 PM10, PM2.5, as well as meteorological factors (temperature and relative humidity).
- Outdoor and indoor PM and chemicals at participants' households.