

CLINICAL STUDY PROTOCOL

**EpiHealth
(Epidemiology for Health)**

– A multicenter longitudinal cohort study

A Lund-Uppsala University collaborative project

UCR Project No: U-10-012

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The clinical study will be conducted, and essential documentation archived, in compliance with UCR SOPs and standards, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

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1 LIST OF ABBREVIATIONS

BMI = Body mass index

CRM = customer relationship management system

EpiHealth= Epidemiology for Health

EDAC = EpiHealth Data Access Committee

GP=General practitioner

GWAS= genome wide association study

HDL= High density lipoprotein

LDL= Low density lipoprotein

LIMS= laboratory information management system

UCR= UPPSALA CLINICAL RESEARCH CENTRE, SEE [HTTP://WWW.UCR.UU.SE/SV](http://www.ucr.uu.se/sv)

QoL= Quality of life

2 BACKGROUND INFORMATION

The main diseases affecting the middle-aged and elderly are multigenetic and also have components of life-style. Several attempts have been made to study interactions between genes and life-style factors, but the majority of such studies are hampered by a lack of power to study the interactions between several genes and several life-style components. The largest studies published so far are in the magnitude of some 10,000 subjects and do not have the power to evaluate such multiple interactions.¹⁻⁴ For such a task, samples in the order of several 100,000 subjects are needed. One such Swedish initiative, the LifeGene Study (www.lifegene.se), will recruit 500,000 individuals in the age-range of 0 to 45 years. Obviously, LifeGene will only cover diseases encountered in younger subjects and will not cover the degenerative disorders seen later in life.

EpiHealth aims to build a national resource being a multicenter longitudinal cohort study investigating the interaction between genes and life-style factors in Swedish men and women between the ages of 45 and 75 years old. Participation in EpiHealth consists of two parts – completing a web-based baseline questionnaire and completing physical tests and biological sampling at a test center. The baseline questionnaire provides information about the participants' medical history and life-style and is divided into fifteen sections such as family structure, education, physical activity etc. The baseline questionnaire can be completed at home by logging in to a personal webpage at www.epihealth.se. Computers for completing the questionnaire will also be available at the test center. At the EpiHealth Test Center, physical measurements and blood samples are collected to provide baseline data such as the participants' cardiovascular status, lung and cognitive functions for more detailed information see Section 2. The EpiHealth database will be merged with the Swedish registries specified in Section 12.2 in order to investigate the EpiHealth objectives (Section 3).

Recruiting of subjects to the EpiHealth cohort study will begin in Uppsala and Malmö, in April of 2011. The study will begin with a pilot phase of 5,000 subjects that will be evaluated after including about 1,000 subjects. An additional ethical

approval application will be sought for the remaining subjects in the fall of 2011, while continuing including persons up to 5,000.

A follow-up of the cohort, for example each 5th year, following the baseline investigation regarding information that could be obtained by the web-based questionnaire is planned. If economically feasible, a follow-up test center visit, for example each 10th year, is planned.

2.1 EPIHEALTH CONSORTIUM

The EpiHealth cohort study is performed by the Lund-Uppsala University collaboration regarding epidemiology (EpiHealth) that has recently been appointed by the Swedish Research Council the status of a "centre of excellence" regarding epidemiological research and is committed to large scale projects in the future.

EpiHealth is governed by the Steering Committee with representatives from Uppsala and Lund Universities. The Steering Committee is responsible for the performance and conduct of the study.

The EpiHealth Data Access Committee (EDAC), appointed by the Steering Committee, will review applications for withdrawal of data and samples from the EpiHealth database and biobank, respectively. An Ethical Committee approval is a prerequisite for an approval by the EDAC.

The study will start with two centres, Uppsala and Malmö, but the intention is to open up centres in other towns in the future to obtain a geographical spread and to collaborate with the LifeGene Test Centres.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

The primary objectives of the EpiHealth cohort study is to provide a resource to study interactions between genotypes and life-style factors in a large cohort (300,000 individuals) derived from the Swedish population in the ages 45 to 75 years regarding the future development of common degenerative disorders, such as myocardial infarction, stroke, heart failure, fractures/osteoporosis, dementia, obstructive lung disease, osteoarthritis/pain, obesity/type 2 diabetes, and cancer.

3.2 SECONDARY OBJECTIVES

Secondary objectives of EpiHealth are:

1. To study prevalences of common degenerative disorders in the Swedish population in the ages 45-75 years.
2. To study life-style patterns in the ages 45-75 years and differences between gender.
3. To study heritability of common degenerative disorders in the Swedish population by using data from families attending both EpiHealth and LifeGene.
4. To evaluate novel biomarkers in serum and plasma for future common degenerative disorders.
5. To study the relationships between genotypes and future development of common degenerative disorders.
6. To study the relationships between life-style factors and future development of common degenerative disorders.

3.3 ENDPOINTS

Since the EpiHealth resource intends to be used to study several of the common degenerative disorders seen in middle-age and in the elderly, no primary endpoint is identified. Instead, eleven different prioritized areas of research have been identified with different specified endpoints within each area:

1. Cause-specific and overall mortality - Death
2. Cardiovascular – Myocardial infarction, stroke, heart failure, atrial fibrillation, aortic aneurysm, hypertension
3. Pulmonary – Chronic obstructive pulmonary disease, sleep-apnea syndrome
4. Osteoporosis – Bone fractures
5. Cancer – Different incident cancers
6. Diabetes/obesitas – Diabetes, BMI, metabolic syndrome
7. Cognitive function – Dementia, cognitive function tests
8. Psychiatry – Depression, anxiety
9. Pain – Self-assessed pain, osteoarthritis, joint replacement
10. Functional capacity - Self-assessed by questionnaire
11. Quality of Life – Self-assessed QoL by questionnaire

4 STUDY DESIGN

4.1 STUDY OUTLINE

EpiHealth is a population-based, multicenter longitudinal cohort study in subjects aged 45-75 years in which exposures (life-style factors and genes) are collected at a baseline investigation.

The study consists of three parts:

1. A collection of data on life-style factors by self-assessment through an internet-based questionnaire.
2. A visit to a test-centre where blood is collected and some physiological parameters are recorded.
3. The population is followed for occurrence of future endpoints defined from the eleven prioritized research areas (see Section 3.3).

Repeated collection of data on exposures i.e. web-based questionnaires and test center visits are planned for examples each 5th and 10th year, respectively, following the baseline investigation.

4.1.1 STUDY OUTLINE AND OBJECTIVES OF THE PILOT PHASE

The pilot phase is planned to include the first 5,000 subjects. The objectives of the pilot phase will be investigated in the initial 1,000 participating subjects, thus enabling a smooth transition between the pilot study and the main study. Alterations of study design and conduct based on the results of the pilot phase evaluation will result in an additional Ethical Committee application for the continuation of EpiHealth (n=300,000 subjects) whilst the EpiHealth pilot phase is ongoing (up to n=5,000). Thus, no break between the pilot phase and the main study in the centres performing the pilot study is planned.

The objectives of the pilot phase are:

1. To test the logistics of the study
 - 1a. Participation rates in the different age-strata.
 - 1b. Collection of fasting blood samples at a test centre visit separate from the collection of the rest of the data using drop-in time and “short-visits”.
2. To evaluate the feasibility to answer the questionnaire by age.
3. To evaluate the instruments used at the test centres to measure physical variables in order to optimize the rest of the study.

It should be pointed out that we do not expect any major alterations in the collection of data to be changed from the pilot phase to the main study, so the data collected in the pilot phase would be included in the main study. Thus, from that perspective the subjects investigated in the pilot phase will contribute, as much as the following participants, to the results in the study.

4.2 SELECTION AND WITHDRAWAL OF SUBJECTS

4.2.1 RECRUITMENT OF PARTICIPANTS

A randomization procedure will assure that all age-groups and both genders are equally represented in the main study. The majority of the sample will be included based on population-based randomization using official registries and/or commercial

address databases. Only people with an address in Sweden and with a Swedish personal security number (personnummer) will be recruited.

A part of the cohort in the main study will be included based on the fact that their children/grandchildren have been included in the LifeGene cohort.

In the pilot phase, an equal number of male and female subjects will be invited to the Uppsala Test Center using the following age-strata; 45-49, 50-54, 55-59, 60-64, 65-69, and 70-75 years. In Malmö, there will be an collaboration with the aortic aneurysm screening program, so that a random number of subjects undergoing ultrasonographic evaluation of the abdominal aorta will be offered to be included in the EpiHealth cohort at the same visit. Thus, in Malmö only male subjects aged 65 years living in the southwest of Skåne will be included in the pilot phase. This is due to economical constrains on the Malmö part of the project. In the main study, however, the Malmö Test Centre will gradually also include women and participants from other age-groups.

4.2.2 INCENTIVES USED TO RECRUIT PARTICIPANTS

Participating subjects will not be offered any financial compensation for participating in EpiHealth.

4.2.3 SUBJECT INCLUSION CRITERIA

Eligible are subjects living in the catchment area of the test centers in the ages 45 to 75 years with a Swedish personal security number.

4.2.4 SUBJECT EXCLUSION CRITERIA

Not willing to participate.

Subjects having no Swedish personal security number.

5 INVITATION AND ENROLLMENT

5.1 INVITATION OF PARTICIPANTS

Potential participants in the age group 45 to 75 years will receive information about EpiHealth and an invitation to participate in the study by postal mail. The postal invitation will consist of:

1. Letter of invitation with activation codes and instruction on how to enroll to EpiHealth on the website www.epihealth.se or via EpiHealth Service Center.
2. Brochure about EpiHealth including general information about EpiHealth, the two parts of the study (questionnaire and test center visit) and also information about the informed consent.
3. The Informed Consent form.

Information on how to get in contact with EpiHealth will be clearly stated both in the letter of invitation and information brochure.

Invitation letter to the Uppsala and Malmö Test Centers, see Appendix 1 and 2, respectively, EpiHealth brochure, see Appendix 3 and Informed Consent form, see Appendix 4.

5.2 ENROLLMENT VIA THE WEBSITE

A subject who wants to participate in EpiHealth will be instructed to visit www.epihealth.se and log on using the activation code supplied in the invitation letter. The activation code is unique and can only be used once. Following activation of the EpiHealth account the participant can enroll to EpiHealth and the web-enrollment process is described in detail below. During web-enrollment participants must supply their personal security number, home address, e-mail address, home and mobile phone number (if applicable).

The website will contain general information about EpiHealth and detailed information about the consent and how to partially or completely withdraw consent and this information will be publicly accessible.

Participants can also, if preferable, contact EpiHealth Test Center that can help with enrollment upon their request.

5.2.1 INITIAL CONSENT FOR HANDLING OF PERSONAL DATA (PERSONNUMMER)

An initial consent is sought at the website following activation using a check-box where the participant confirms participation and that he or she has read and understood the consent agreement. The participant recognizes that personal data (personnummer), home address, e-mail address and mobile and home phone number will be stored and used by EpiHealth. Once at the test center the participant will sign a formal written consent which is a prerequisite for EpiHealth to use any data generated by the baseline questionnaire and results from the test center visit. See Section 6 for more information about the EpiHealth formal written consent.

5.2.2 SCHEDULING OF VISIT TO TEST CENTER

Participants will schedule a time for the visit to the test center. At the website there will be a calendar function for scheduling test center visits. A confirmation of the scheduled visit to the test center will be sent via e-mail. In addition, a reminder, via SMS, will be sent to the participant 24 hrs prior to the test center visit (if applicable).

5.2.3 THE BASELINE QUESTIONNAIRE

As soon as the initial consent is given, participants will be able to start answering the EpiHealth baseline questionnaire presented at www.epihealth.se. The questionnaire is described in detail in Section 8.1.

5.2.4 FEEDBACK TO EPIHEALTH

EpiHealth constantly seeks to improve. Therefore, participants will have the opportunity to provide feedback to EpiHealth through, e-mail or by phone to the EpiHealth Test Center.

5.2.5 FEEDBACK FROM EPIHEALTH

EpiHealth will provide follow-up to participants on certain results if he or she has given consent to do so. The results will include physical measurements performed at the test center and some laboratory results from blood sample analyses. The feedback will mainly be provided through the website. The kind of feedback that will be given and the methods that will be used to do so are described in Section 9.

5.2.6 DECLINE PARTICIPATION

A subject invited to participate in EpiHealth can decline to enroll by contacting EpiHealth Test Center. He or she may also choose to not act on the invitation at all. If the invited subject has not made clear his or her desire to participate (or not participate) within 10 days from when the initial invitation was sent out, one reminder may be sent out. If the participant does not act on the reminder it is assumed that he or she is not interested in participating.

6 INFORMED CONSENT

6.1 GENERAL PRINCIPLES

It is important for EpiHealth to make sure that participants understand what they are consenting to when they agree to take part. This will be done with transparent and easy-to-understand communications and by ensuring that EpiHealth personnel are trained in communicating the information and assessing the understanding of participants. In addition, studies approved by EDAC will be announced at www.epihealth.se one month prior to study start.

The consent to participate in EpiHealth will apply throughout the lifetime of EpiHealth unless the participant chooses to withdraw.

6.2 FORMAL WRITTEN CONSENT

An initial consent for handling of personal data will be obtained during the online enrolment via a check-box (or a similar mechanism) on www.epihealth.se.

A formal written consent will be sought from participants in EpiHealth during the first visit to the test center. The potential participant will be given detailed information about formal written consent by personnel at the test center. The main purpose of EpiHealth is to enable scientists to apply for analysis of data and/or samples from the EpiHealth database and biobank, respectively. Therefore the consent given by the participant is a broad consent comprising of consent to 1) handle personal data and save results from the questionnaires and test center visits, 2) biobank blood samples, 3) biobank DNA, 4) use data and samples collected for health related research approved by a Ethical Committee, 5) merge with official registries and national quality registries to gain the information specified in the EpiHealth information brochure, 6) merge with medical records and that the participant has been informed about the possibility to partially or completely withdraw the consent without further explanation.

The formal written consent form given at the test center is included in Appendix 4. Answering questions concerning the consent will be done by the personnel at the test center. The consent will be scanned and stored in a secured manner.

The letter of invitation will contain information about consent and withdrawal. The Epihealth website will contain more detailed information about consent.

6.3 PARTIAL OR COMPLETE WITHDRAWAL OF THE FORMAL WRITTEN CONSENT

The consent can be partially or completely withdrawn upon request by the participants, i.e. the participant can choose to restrict the informal written consent to withdraw consent to:

- **“Blood sample withdrawal”**: EpiHealth will not use stored blood samples collected in the biobank.
- **“DNA withdrawal”**: EpiHealth will not use DNA collected in the biobank.

- **“Official registries withdrawal”**: EpiHealth will not merge collected data with official registries and quality registries in order to gain the information specified in the EpiHealth information brochure.
- **“Medical records withdrawal”**: EpiHealth will not merge collected data with medical records.
- **“No further contact”**: EpiHealth would no longer contact the participant or obtain further information from their health-relevant records in the future, but would still have their permission to use the information and samples provided previously.
- **“Complete withdrawal”**: In addition to no longer contacting the participant or obtaining further information from records, EpiHealth will completely stop using any health-related information and samples collected previously. Some administrative details (such as their signed consent and withdrawal) would be kept as a record of their wishes, without the possibility to use these samples and data in future research. Such a withdrawal would prevent information about them from contributing to further longitudinal analyses, but it would not be feasible to remove their data from analyses that have already been done.

The Withdrawal of the formal written consent form is included in Appendix 5. The Withdrawal of the formal written consent will be scanned and stored in a secure manner.

The possibility to partially withdraw the consent is clearly stated in the written informed consent (Appendix 4), in the EpiHealth information brochure (Appendix 3) and on the website.

When completely withdrawing, in addition to no longer contacting the participant or obtaining further information from records, EpiHealth will completely stop using health-related data and samples collected previously. If a participant decides to withdraw then EpiHealth would seek written confirmation of the withdrawal from the participant.

Despite EpiHealth's efforts to stay in touch with participants, it may well lose contact with some as they relocate, emigrate, or do not respond to communications. Where a participant has not actively withdrawn, EpiHealth will continue to use the samples and data and maintain linkages, although it will not be able to update some data (e.g. those collected by repeat questionnaires or test center visits).

Analysis of data and/or samples from the database and biobank, respectively, will be possible following approval from the Ethical Committee and the EDAC (Section 2.1) thus the subjects does not know upon inclusion in EpiHealth the specific scientific questions being investigated other than the objectives of EpiHealth (Section 3). For this reason, EpiHealth website will post a short summary of approved study proposals one month prior to data/sample extraction thus enabling the subjects to evaluate the scientific development of EpiHealth and, if preferred, withdraw their participation in EpiHealth.

7 TREATMENT OF SUBJECTS

Since this is an observational study, no uniform treatment is given to the participants. However, a written feedback on the physical and laboratory test evaluated at the test centre will be given to the participants regarding their risk factor profile; blood pressure, fasting glucose, LDL- and HDL-cholesterol and serum triglycerides, heart rhythm, and lung function. In some cases, this feedback will include an advice to the participant to visit their general practitioner (GP) due to some deviation in these risk factors. In some rare cases, the participants will asked to immediately seek emergency care, see below. Furthermore, smokers will be advised to stop smoking at the visit to the test centre.

In order to increase the rate of complete questionnaires, a complete questionnaire is a prerequisite for obtaining feedback on the physical and laboratory test from EpiHealth. However, in cases where physical and laboratory test urge participants to immediately seek emergency care, feedback will be given even if the subjects have incomplete questionnaires.

8 ASSESSMENT OF EXPOSURES

8.1 EPIHEALTH QUESTIONNAIRE

The baseline questionnaire is answered by logging on to a personal webpage at the EpiHealth website (www.epihealth.se). The participant can answer the whole questionnaire at one time or complete it in parts at different times when it suits him or her best. The questionnaire is about life-style factors divided into fifteen sections. The estimated time to complete the form is 40 minutes. Computers will be available at the test center for participants that wish to answer the questionnaire at the test center and for subjects that need computer assistance. The baseline questionnaire is customized depending on gender and is hierarchically branched based on the participant's answers. EpiHealth has done extensive work in making the baseline questionnaire as user friendly as possible. The baseline questionnaire is constructed in such a way as to minimize participant burden, i.e. by minimizing the number of questions being asked. This is done by using a branching structure that optimizes the number of relevant questions to each participant.

The groups of items included in the life-style questionnaire are the following:

1. Family structure
2. Social group
3. Education
4. Reproduction
5. History of diseases
6. Medication usage
7. Food intake
8. Alcohol consumption
9. Smoking/Snuff history
10. Physical activity
11. Work life history
12. Pain history
13. Quality of Life
14. History of injuries

15. Environmental exposures

See Appendix 6 for the baseline questionnaire.

8.2 ASSESSMENT AT THE TEST CENTRE

When participants arrive at the test center they will be welcomed by a receptionist. The receptionist will ask to see an identify card and confirm this to the datasystem. The receptionist will provide information, both written and verbal, about the following:

- General information about EpiHealth and the consent process
- Why the participants contribution is valuable to EpiHealth
- Which test will be carried out and how
- Informed those participants that have not completed the questionnaire that this is a prerequisite for obtaining feedback from EpiHealth

8.2.1 SIGNING OF THE FORMAL WRITTEN CONSENT

Consent will be signed at EpiHealth Test Center where it is scanned and stored in a secure manner, see Section 6.2.

8.2.2 PHYSICAL MEASUREMENTS AT THE TEST CENTER

Following the signing of the formal written consent, the receptionists will take a simple 1-lead ECG by contact between the participant's hands and ECG electrodes (Zenikor-EKG, Zenicor, Sweden) to screen for atrial fibrillation and some other more rare arrhythmias.

Upon completion of the ECG, the participant is directed to a computer and will be given a short introduction to the Trail making B test¹. Once the test has been

¹ The Trail making B test records the time to draw a line between certain letters and numbers. Maximum time: 5 min.

completed, a member of the EpiHealth testing staff will meet up with the participant and take him or her to the test room.

The participant will be asked the following questions by the staff, the results of which will be entered in the LIMS:

- Have you had a current infection/inflammation within the last two weeks? Yes/No
- Have you eaten today? Yes/No
- Do you have atrial fibrillation? Yes/No
- Do you take any medication for high blood pressure? Yes/No
- Do you take any medication for high cholesterol? Yes/No
- Do you take any medication for diabetes? Yes/No
- Do you want feedback on your physical test and blood test results? And do you want your feedback delivered to you via personal website or postal mail?

Physical tests performed in the test room:

- Blood pressure and pulse rate are recorded twice in the sitting position by an automatic device (Omron Kyoto, Japan).
- Height is recorded and waist circumference is measured at the umbilical level.
- Weight is recorded at a scale that uses bioimpedance to calculate fat mass (Tanita, Tokyo, Japan).
- A simplified lung function test is performed to measure FEV1 and VC (MiniSpir, MIR Medical International Research, WI, US).

8.2.2.1 Biological sampling

At the test centre, 100 ml of blood is taken. 90 ml are prepared into plasma, serum and whole blood (for later DNA extraction) and stored in a biobank facility for later analysis. 10 ml are used for determinations of:

1. fasting glucose,
2. LDL- and HDL-cholesterol
3. serum triglycerides

These measurements are analyzed at the test centre using a point-of-care instrument (Cholestech LDX, Cholestech[®], CA, US) alternately at the local clinical chemistry laboratory. LDL-cholesterol is calculated from HDL and triglycerides using the Friedewald's formula. In case of Cholestech failing to measure, the samples will be sent for analyses at the local clinical chemistry laboratory. Quality controls of the point-of-care instrument will be performed regularly.

All measurements are either transmitted online or entered into the database at the visit by the staff. A bar code will be used for this purpose, as well as for the identification of the samples to be frozen.

8.2.3 TERMINATION OF THE TEST CENTER VISIT

Before termination of the test center visit the personnel will inform the participant of the following:

- That the results from the blood analyses and the ECG will be accessible within three weeks at the EpiHealth website if he or she consented to receiving the follow-up information and has completed the baseline questionnaire. To access the follow-up information the participant has to log on to his or hers personal EpiHealth the page. The EpiHealth staff will stress the importance of completing the baseline questionnaire, but will also clearly point out that values urging immediate care will be notified to the participant regardless of the status of their questionnaire.
- That the EpiHealth Test Center can answer any future questions and inform of the opening hours.
- That, in the future, there might be sub-studies of EpiHealth and would the participants consent to be contacted regarding inclusion in any of these sub-studies (if so, a note of this will be made in the EpiHealth CRM system).

8.2.4 HANDLING OF BIOLOGICAL SAMPLES

The biological samples will be transported to a biobanking facility where pre-processing, storage and post-processing will be conducted. The following samples will be sent for biobank storage:

- Whole blood
- DNA (if applicable).
- Serum
- Plasma

9 FEEDBACK TO THE PARTICIPANT

If consented to, follow-up information from the test center will be available on the participants personal EpiHealth page at www.epihealth.se within three weeks given that the subject completed the baseline questionnaire. Participants indicated that they wish to receive their feedback via written feedback will receive this via the postal mail. The feedback will include the actual figures, reference values and recommendations on actions to be performed, if so, in most cases a visit to the GP.

Cut off values used for recommendations:

1. Fasting plasma glucose >7.0 mmol/l. A new value recommended within a couple of weeks.
2. LDL >3.5 mmol/l. Decision about dietary treatment/lipid lowering therapy needed within 2 months.
3. Serum triglycerides >2.0 mmol/l. Decision about dietary treatment/lipid lowering therapy needed within 2 months.
4. Blood pressure $>140/90$ mmHg. A new value recommended within a couple of weeks.
5. A FEV1 $< 70\%$. A visit to the GP recommended within a couple of weeks if a diagnosis of asthma or COPD is not known.
A FEV1 $< 50\%$. A visit to the hospital pulmonary clinic will be initiated from the test centre if a diagnosis of asthma or COPD is not known.

For blood pressure $>180/110$ or fasting plasma glucose >10.0 mmol/l, the subjects will be contacted within days with a recommendation of a rapid check-up by their GP. The ECGs will be evaluated by a physician. If the ECG is not technically good enough for an evaluation, the subjects will be asked to return for a new ECG using other leads for registration (hand to foot). A finding of an unknown atrial fibrillation, the subjects will be contacted within days with a recommendation of a rapid check-up by their GP. If the rate of atrial fibrillation is >100 , the subject will be referred to the emergency department.

Before the feedback information is sent to the subject, a medically trained professional will revise the data to ensure that rescue values are appropriately taken care of. Feedback urging immediate care will given by phone. If the participant cannot be contacted by phone, the message will be sent both via postal mail and the personal EpiHealth page. The reason for double posting is to increase the possibility that the participant in question will receive the information as soon as possible.

The subjects will not receive any feedback regarding genetic analysis or analysis of blood samples stored in the biobank and later analyzed.

10 ASSESSMENT OF OUTCOMES

In most cases endpoints will be collected by merging the database with the official registers specified in Section 12.2, such as the Swedish cancer register, the Swedish cause of death register, and the Swedish in-hospital care registers. In some other cases, endpoints will be collected through hospital or primary care records or by different national quality control registers (such as riks-HIA, riks-STROKE etc). Hospital or primary care records might also be needed for the validation of the correctness of diagnosis in the official registers.

11 ANALYSIS OF BIOMARKERS AND GENOTYPING

Approximately 90 ml of the withdrawn blood volume will be processed to serum and plasma and divided into small fractions and stored in a biobank facility for later analysis. The usage of this material will be later determined by the EDAC according to the requests of the research proposals. Most likely, a single biomarker will not be analyzed in the total sample, but rather on a nested case-control basis. Thus, in order to gather a certain number of events, the analysis of most samples are most like not to occur during EpiHealth's first years.

If economically possible, DNA extraction will be performed as soon as possible following whole blood withdrawal otherwise whole blood will be stored for later DNA extraction. Due to the rapid development of genotyping it is believed that the Gold Standard Genome Wide Association Scans (GWAS) of today will be replaced by other more powerful genotyping techniques (read sequencing) by the time of analysis. Also the analysis of epigenetics will possibly develop in a rapid pace. Also in this context, analysis will be performed by the state-of-the-art methods at the time of analysis.

12 STATISTICS AND DATA MANAGEMENT

12.1 DATA MANAGEMENT

The data will be collected by the same data system used by the LifeGene study. The data will then be handled by a specific data manager at UCR to build a database and to merge the database with official registers regarding endpoints, exposures, medication usage etc.

12.2 REGISTERS

The EpiHealth database will be merged with several Swedish registers, namely:

1. *Swedish Population Registry*; regarding address, place of birth, parents place of birth and marriage
2. *Swedish Censuses (1960-90)*; regarding social group, income, living conditions, education
3. *Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier (LISA) (from 1990)*; regarding employments and sick leave
4. *Swedish National Insurance Agency*; regarding sick leave.
5. *Utbildningsregistret (UREG)*; regarding education
6. *Swedish Multi-Generation Register*; regarding family members
7. *Medicinska födelseregistret (MFR)*; regarding pregnancies and deliveries, birth-weight
8. *Swedish Patient Registry*; regarding in-hospital care
9. *Swedish Prescription Registry*; regarding use of medication
10. *Swedish Cause-of-Death Registry*; regarding vital status and cause of death
11. *Swedish Cancer Registry*; regarding cancer
12. *Outpatient Registries*; regarding care in primary care facilities (includes *Day Surgery Registry*)
13. *Swedish military service conscription register*; regarding blood pressure, exercise capacity, body height and weigh
14. *Swedish Information System on Occupational Accidents and Work-related Diseases*; regarding occupational accidents and work-related diseases

Today over 50 national quality registries exist for quality control of the care of different diseases. It might be relevant to merge the EpiHealth database with some of these registers in the future.

12.3 STATISTICAL ANALYSIS

No data or samples of the EpiHealth resource will be analyzed without two premises. One is an approval from the EpiHealth Data Access Committee which reviews study proposals from researchers. The other is an approval from the Ethics Committee regarding the intended analysis.

An exception from these rules is logistical and quality checks that will take place regularly throughout the study to assure proper logistics and a high quality of the study. These statistical analyses are however not primarily linked to the research questions and only used for internal purposes.

13 ETHICS

13.1 INDEPENDENT ETHICS COMMITTEE

Approval by the Ethics Committee should be sought 1. Before the start of the pilot phase of the study. 2. At the start of the continuation of the study, called main study. 3. At each time a statistical analysis or sample withdrawal from the biobank is to be performed according to the decision of the EpiHealth Data Access Committee.

The merging of the EpiHealth database with official Swedish registries (not including national quality registries) is however regarded as a part of the informed consent.

13.2 PATIENT INFORMATION AND INFORMED CONSENT

See Section 5 and 6.

14 SUB-STUDIES

As stated previously, following permission from the EpiHealth Data Access Committee (EDAC) and the Ethical Committee, researchers could choose to invite subgroups of the EpiHealth cohort to secondary visits with a more careful phenotyping or to share data with other studies including EpiHealth participants. These substudies should be financed by the researcher proposing the substudy and not by the EpiHealth cohort study.

15 ACCESS TO THE EPIHEALTH RESOURCE

Access to the EpiHealth resource, i.e. database and samples, is only given for research purposes. EpiHealth requires that access requests include a scientifically sound and ethically appropriate research plan. These will be ethically and scientifically peer reviewed and approved by EDAC and a Ethical Committee (Etiprövningsnämnd). All proposals will be reviewed by EpiHealth to ensure they are consistent with the participants' consent and the ethics policy of EpiHealth (Appendix 7), and that they have relevant ethics approval. All users, whether employed by universities, government, charities, or commercial companies, will be held to the same scientific and ethical standards. Commercial interests of researchers will be irrelevant in determining access to the resource.

In cases of international researchers applying for access to EpiHealths database and/or samples, EpiHealth will act in accordance with the Swedish Biobank Act [chapter 4, §3] and require a Swedish research institution to file for approval for sharing biological samples outside Sweden. International researchers will be held to the same standard as Swedish researchers regarding access and usage of EpiHealth resources. All researchers (Swedish and international) need to sign a contract clearly stating the obligations of EpiHealth and the researcher.

Use of the biological samples will have to be carefully coordinated and controlled because they are limited. While the resource is being developed, EpiHealth may use the early data and samples to validate and improve methods of data collection and

analysis. The general criterion for such a priority is the scientific and potential health value of the research projects in question, as judged by EDAC.

Researchers will be provided access only to biological materials, data or information that is coded such that the participant cannot be identified and researchers will be required by the contract not to attempt to re-identify participants. Different mechanisms will be employed to ensure that researchers are not inadvertently provided access to potentially identifying data, for instance by not giving more data than what is relevant to the research project in question. Users of data will sign confidentiality agreements.

EpiHealth will only transfer specimens and data when there are adequate standards in place regarding privacy of the participant and confidentiality of the data, safety and good laboratory methods, and in accordance with applicable law and regulations.

If a research group wants to target specific subgroups for research, identification of such groups is performed by EpiHealth, maintaining the confidentiality of the participants. Such subgroups can be defined e.g. by results of physical measurements or blood analysis; as well as based on disease status or data from registries. Re-contact with selected participants will in general be performed only by EpiHealth. Research projects that want to contact specified subgroups will have to be approved by an Ethical Committee. Although participants will be re-contacted by EpiHealth in order to provide e.g. changes in health status, EpiHealth will act to ensure that re-contacting is not unduly burdensome for participants. If participants feel that re-contact is too burdensome or intrusive, they have the option to withdraw their participation to various degrees as described in Section 6.3.

All research users will be required to put results from all analyses made on participants' data and samples, and any relevant supporting information, in the EpiHealth database so that they are subsequently available to all researchers with appropriate scientific and ethical approval. EpiHealth will require results to meet a standard of quality for incorporation into EpiHealth's database.

There will also be a requirement on research users to place the findings (whether positive or negative) from research based on EpiHealth data/samples in domains that

can be accessed by the public so that people can benefit from the findings. Publication should be in peer-reviewed scientific literature whenever possible.

Researchers will only be permitted to keep results based on EpiHealth confidential for a limited and reasonable period (for example while they prepare papers for publication, file patent applications, or otherwise pursue reasonable competitive advantage for their efforts). This policy will apply to all research users, whether non-commercial or commercial.

Researchers should acknowledge EpiHealth in publications, presentations, and patents filed as being the resource they used in the research in question. EpiHealth will provide researchers using its resources with detailed guidance on the manner in which it wishes to be acknowledged.

16 DATA HANDLING

The data handling and system in EpiHealth is the same as in LifeGene.

Because EpiHealth will store personal data in a central database, it is defined by Swedish legislation as a person register and must be administered according to the Personal Data Act (PDA, Personuppgiftslagen, PuL 1998:204). PDA legislation aims to protect individuals and their personal integrity. Any kind of information that directly or indirectly could be assigned to a physical person that is alive is personal data. All data in EpiHealth, except the metadata, is considered to be personal data and is thus treated according to the relevant law. The metadata consists of information about which instruments were used for testing and how the questionnaires were designed.

The database holding research data will be stored separately from the administrative database holding identifying information (the CRM). Only a few people within EpiHealth will have access to the database.

EpiHealth will establish and maintain an information security management system based on the standard SS-ISO/IEC 27000. This will ensure that the proper processes,

routines and methodology are in place for continuous work regarding information security.

16.1 CONTACT AND CONSENT DATA

Potential participants will be identified via Swedish national registers. EpiHealth will need to hold identifying information (such as name, address, birth date, personal identity number) to invite and handle participants. Some of the information will be updated on a regular basis in order to contact only living persons at correct addresses.

Identifying information such as contact information, consent status and progress status will be stored in the system for participant management - CRM. A customer relationship management system (CRM) is the software that EpiHealth will use to track and organize its communication with current and prospective participants. Access to information about participants and potential participants is thoroughly regulated via administrative groups. The administrative groups have different levels of permissions to participant data (read, write, add or delete participants); this functionality is standard in the CRM-system used. Only authorized EpiHealth personnel have access to the CRM system and each user will have a unique username and password to enable traceability.

A complete back-up of the EpiHealth database is performed every 15 minutes and in addition is every activity recorded in a separate log file.

16.2 COLLECTION OF RESEARCH DATA

During the baseline, data collection will be from three primary sources: webbased questionnaires; physical measurements from the EpiHealth Test Center visits; and results from the analysis of blood before storage.

The database management system used is a reliable and time-tested system with controlled access as a standard functionality. The servers are stored in a safe data hall with procedures for physical security and protection (e.g. fire, water, burglary,

electricity). Only specific IT operation staff members have physical access to the data hall.

All data from the questionnaires, physical measurements from the test center visits and blood sample analysis will be stored in the central database. The transfer of data from the questionnaires, the test center visits and the biobank to the database will be done automatically via encrypted communication protocols. The validity of measurements and answers to the questionnaires will be checked during the collection of the data. Logical controls used to ensure the validity of data include, for instance, that personal events must have occurred after the date of birth and that answers are within a normal range.

At the EpiHealth Test Center stations, the physical measurements will be supported via a LIMS system (Laboratory Information Management System). The instruments used for measurements will be connected to the LIMS system, where results will be stored. When electronic transfer of data to the database is not possible, manual data transfer to the LIMS system will be applied. When all data has been collected it will automatically be sent to the central database. Since all systems are client/server based, data is not stored at the test center. Along with the resulting data, metadata will also be sent describing e.g. the date, time and version of the instrument used.

Data from the initial analysis of blood will be electronically transferred from the central laboratory to the central database, via the LIMS system.

16.3 CONFIDENTIALITY, SECURITY AND INTEGRITY

EpiHealth will maintain strict measures to protect confidentiality, and will ensure that data and samples are handled and stored to very high standards of security. The same protection will be extended under contract for any handling or analysis of data or samples by third parties engaged to provide services necessary for developing the resource.

16.3.1 CONFIDENTIALITY

All identifying information will be held centrally by EpiHealth in a restricted-access database that will be controlled by senior EpiHealth staff.

Research users will be given access to anonymized data and samples. Neither the personal identification number nor the study identification number will be used when an external research group has been granted access to data. Each individual research project will have new randomized identification numbers, making it impossible to compile data from different projects. Each project will be given access to data on a need-to-know basis, that is, only to the data necessary for that research question.

16.3.2 SECURITY AND INTEGRITY

The integrity of the information has to be guaranteed from data collection to analysis. All data is protected against unauthorized access through authentication processes and encryption of data transmissions. Permission to access data will be restricted - this applies to researchers as well as EpiHealth personnel. EpiHealth has an access policy aiming to hinder illicit usage. All users of data will have to sign personal data assistant contracts. The correctness of the information is ensured by regular backups and all changes in the data are logged to ensure full traceability.

A wide variety of measures will be taken to ensure the security of data, samples, the database and the information technology system in general. These include staff training and confidentiality contracts, physical and electronic controls on access to data, internet security, and physical security. This should prevent identifiable information from being used – inadvertently or deliberately – for any purpose other than approved research.

17 QUALITY CONTROL AND MONITORING

All human biological materials and data will be subject to proper quality control and quality assurance measures at every stage of its processing including procurement, collection, labeling, registration, storage, tracking, retrieval, dissemination, use and destruction in order to ensure high standards of quality in all EpiHealth resources.

EpiHealth will establish and maintain a defined and documented quality management system. This system will:

- Ensure that the operation and control of quality management process are effective.
- Assure the availability of resources (staff, facilities, and equipment) and information (standard operating procedures) necessary to support the operation of the processes involved in sample and data collection.
- Measure, monitor, and analyze these processes.
- Implement actions necessary to achieve planned results and continuous improvement.

Where appropriate the EpiHealth quality management system will conform to requirements and recommendations in:

- ISO 9001:2000 Quality Management System – Requirements.
- ISO 17025:2005 General Requirements for the Competence of Calibration and Testing Laboratories.
- OECD Principles of Good Laboratory Practice.
- ICH Guideline for Good Clinical Practice.

The EpiHealth quality management system will be regularly evaluated by internal and external audits.

18 REFERENCES

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19 APPENDIX

- Appendix 1 Letter of Invitation - Uppsala
- Appendix 2 Letter of Invitation - Malmö
- Appendix 3 EpiHealth Information Brochure
- Appendix 4 Informed Consent Form
- Appendix 5 Withdrawal of Consent Form
- Appendix 6 Baseline Questionnaire
- Appendix 7 EpiHealth Ethical Policy