

KTL/ULTRA/EU Environment and Climate contract No ENV4-CT97-0568
 THE FLOW OF THE CLINICAL VISIT IN ULTRA 2 STUDY

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The flow of the clinical visit in ULTRA 2

1. PURPOSE AND APPLICABILITY

The purpose of this SOP is to ensure that the clinical visits within ULTRA 2 study are conducted in the same way by each field worker in each participating center. This SOP should be followed in every clinical visit in ULTRA 2 study.

2. DEFINITIONS

KTL: National Public Health Institute, Finland

PI: principal investigator

ECG: electrocardiography

3. REFERENCES

ULTRA 2 study manual.

OMRON® M4 Instruction manual

SOP of spirometry in ULTRA 2 study, SOP ULTRA/ UoW - F - 1.(*

SOP of ambulatory ECG (Holter) recordings in ULTRA 2 study, SOP ULTRA / KTL - F - 1.(*

*) This statement refers to the latest SOP revision available. Make sure that you know and have it.

4. DISCUSSION

N.A.

5. RESPONSIBILITIES

KTL is responsible for the developing and editing the contents of the SOP for the clinical visit (ULTRA/KTL - F - 2.0). Any person who changes this procedure is responsible for ensuring that the change has been properly documented, the SOP changed, reviewed and approved by the local principal investigator(s).

The PI:s in each center are responsible for implementation of this SOP.

6. EQUIPMENT AND MATERIALS

- a) equipment: refrigerator for storage of urine samples (-18 °C), heart rate monitor (e.g. Polar Electro), blood pressure monitor (Omron M4), equipment listed in SOPs for ambulatory ECG (ULTRA/KTL-F-1.0), spirometry (ULTRA/UoW-F-1.0), bicycle ergometer
- b) paper materials: clinical visit log book / questionnaire, stickers for labeling the urinary sample tubes, pencils
- c) materials: see SOPs for ambulatory ECG (ULTRA/KTL-F-1.0), spirometry (ULTRA/UoW-F-1.0), for urine samples: collection container, 5 ml polyethylene tubes

7. PROCEDURE

7.1. General

The subjects will have a clinical visit every two weeks. For each subject, the visit is aimed to be always on the same weekday at the same time (± 1 h). If this is not possible, e.g. because of an illness, the next choice is to move the particular visit to another day at the same time. When the latter is also impossible, the clinical visit should be placed whenever possible. During the visit, autonomous nervous system will be stimulated by paced breathing (parasympathetic stimulation) and standing up from supine position (sympathetic stimulation), urine samples will be collected, spirometric lung function of the subject will be measured, and electrocardiography (ECG) will be recorded over the time of the visit. The visit includes also a at least 6-minute exercise challenge at own pace aiming at 90 - 100 beats/min. The field worker, e.g. a nurse, will take care of the visit, but a consulting physician should be easily available.

7.2 Medication

There is no need to modify daily medication because of the clinical visit with the exception of short-acting medication for respiratory diseases (asthma). The detailed instructions of the medication use are in the SOP for spirometry (ULTRA/UoW-F-1.0). Medication use prior to spirometric testing and ambulatory ECG monitoring should be carefully documented. Medication use is not a criterion for not conducting the measurements, however.

7.3 Precautions, contraindications, safety factors

If the subject has, during the clinical visit or preceding 1 hour symptoms of angina pectoris no spirometry or exercise test must be performed. No exercise must be performed if the subject has moderate or severe respiratory symptoms (wheezing, shortness of breath, asthma, COPD) during the clinical visit or preceding 1 hour, or fever during the preceding week. A common cold or respiratory infection are relative contraindications for the exercise, and the field worker should use 'common sense'. The exercise must be stopped if the subjects wants to, gets symptoms of angina pectoris, arrhythmia, shortness of breath or hyperventilation, unusual or exceptionally strong fatigue, faintness, pain in legs (claudication), strong muscular, tendon or articular pain, or the performance becomes unstable or coordination of the movements becomes poor.

If spirometry and/or exercise challenge are not performed, the flow of the visit should be

followed, i.e. the urine samples will still be collected, the questionnaire filled in, diary changed, and the ambulatory ECG will be recorded during rest, paced breathing and in standing position. The reason for not conducting or quitting the spirometry or exercise test must be documented in the clinical visit log book.

Safety factors are carefully taken into account during the clinical visits. A physician must be available all the time within minutes. During the first visit, a physician examines and interviews all the subjects, and checks for the inclusion and exclusion criteria. The field worker interviews the subjects in the beginning of every visit. In the clinical visit room, there must be a bed for resting, medication for angina pectoris and asthma symptoms (short-acting nitroglycerin and beta-agonist, respectively), and a possibility to measure blood pressure. In addition, in the beginning of every ambulatory ECG recording, a one-minute ECG is taken using the same electrodes to ensure the ability to perform spirometry and exercise. If new ECG changes occur (new=not present in the strips registered in the previous visits), e.g. ST-changes, arrhythmia, spirometry or exercise will be done only after a physician has been consulted and a permission has been given. The one-minute recording serves also as a part of quality control for the ambulatory ECG recording. In the end of the ECG recording, another one-minute strip will be taken to ensure that no new ECG changes has emerged during the clinical visit and to check the signal of the Holter recording at the end.

7.4 Clinical visit log book and questionnaire

The clinical visit questionnaire is filled in in the beginning of the visit, and the log book is filled in during the course of the visit. The clinical visit log book and questionnaire are attached. The identification code of the nurse conducting a particular procedure must be marked in the log book. The field workers will have an own identification code: 10 - 29 for Amsterdam, 30 - 49 for Erfurt, and 50 - 69 for Helsinki.

7.5 ECG recordings

The ECG recordings are conducted according the respective SOP (ULTRA/KTL-F-1.0).

7.6 Spirometry

The spirometric lung function measurements are conducted according the respective SOP (ULTRA/UoW-F-1.0).

7.7 Exercise challenge

The exercise will last at least 6 min, and it will be done at subject's own pace. The aim is an even heart rate at a level of 90 -100 beats/min. During the first visit, it is checked whether this level can be achieved and an individual level will be set. If only a lower level is possible, this lower individual level will be set and kept be also during the course of the study. The form of exercise could be walking on a treadmill or on a step board, but preferable a bicycle ergometer. The same method must always be used for the same subjects. The heart rate will be monitored during the exercise e.g. with a Polar™ heart rate monitor. The load will be adjusted according the heart rate always taken into account the working capacity of the subject. The exercise could be started at a level of 50 W for men and 40 W for women, and 50 - 60 rpm. The target level will be achieved stepwise. During the first visit, the steps could be e.g. an increase of 10 W every 30 sec, in order to find the individual target level for the next visit. If this seems to be too little, increases of 20 W can be used. During the next visits,

the load is gradually increased to the target load during the first minute of exercise.

7.8 Urinary samples

A spot urinary sample is collected for Clara cell protein CC16 analyses. For the analyses, about 5 ml of urine is needed. However, as prostatic secretions may contaminate the sample, it is important to get a mid-stream sample from male subjects. For females, a 'total' sample will be collected. The spot sample will be collected in a container, and at least 5 ml of urine is transferred in a polyethylene tube. The tube should not be filled to the top. The samples are stored during the day in room temperature, and are put into the refrigerator (-18 °C) in the end of the day for storage.

After the field work, the tubes will be transported to Brussels by express courier on dry ice all at a time. Each center will take care of transporting their samples. The laboratory in Brussels should be informed before sending the samples (e.g. by e-mail: bernard@toxi.ucl.ac.be, with reference to ULTRA-study).

The address is :

Prof. A. Bernard
Unité de Toxicologie Industrielle et de Médecine du Travail
UCL Faculté de Médecine
Clos Chapelle-aux-Champs 30.54
B-1200 Bruxelles
Belgium

7.9 Blood pressure measurements

Blood pressure will be measured with a digitalized monitor Omron® M4. The monitor is prepared for the measurements according the Instruction manual. The cuff is wrapped firmly around the bare right upper arm of the subject so that the green-colored band is positioned 2-3 cm above the elbow joint on the inside of the arm. To measure the blood pressure, follow the instructions in the manual (OMRON® M4 Instruction manual). Set the inflation pre-set switch to a value of 200. The measurement is done two times in supine position, and once in upright position. Keep an interval of at least 45 sec between the repeated measurements. All results are written down in the clinical visit log book.

The digitalized monitor must be compared to a sphygmomanometer by measuring 15 subjects in supine and standing position three times with the digitalized monitor and three times with the sphygmomanometer. After 1 - 2 weeks, the measurements with the digitalized monitor should be repeated in the same subjects. All results must be written down for analyses.

7.10 Breathing frequency measurements

The breathing frequency of the subject is counted by watching the chest movements when the subject is in supine position. Every inhalation is one breath. The counting time is one minute.

7.11 Flow of the clinical visit

The flow of the visit needs to be the same within a center, and even more important is always to follow the same flow within a subject. The flow of the clinical visit will be documented on

a clinical visit data sheet, which includes also the questionnaire. Here is an example of the flow. The steps 3 - 9 must be exactly followed in this order in all centers. The order of the other steps may vary between the centers, however. It must also be noticed that if the exercise test precedes spirometry, there has to be a 15-min rest before the spirometry according the SOP, and Holter monitoring should not start before 15 min has lapsed after the spirometry. The exact time point (since the start of the ECG, measured with a stopwatch) of the start of each procedure must be written down in the clinical visit log book. The 0-point is the time when the tape starts rolling in the Holter recorder, and the time points that will be marked are minutes and seconds from this 0-point.

The pace breathing is paced by the field worker saying to the subject "inhale -2 - 3, exhale -2 -3". The field worker follows the stopwatch or metronome to keep in the frequency of 12 Hz, that is 2.5 sec inhalation and 2.5 sec exhalation.

Steps to follow:

0. Before or together with 1. or after 9.

diary change

collection of the urine sample for analyses of biomarker of lung damage

- | | |
|---------------------|--|
| 1. Sitting position | interview |
| 2. Sitting position | installation of Holter and ECG system |
| 3. Supine position | ECG rhythm strip for 1 min for safety and quality control reasons, start of Holter |
| 3. Supine position | at least a 5 min rest, including measurement of breathing frequency for 1 min, between 3 - 4 min |
| 4. Supine position | paced breathing (2.5 sec inhalation, 2.5 sec exhalation) for at least 5 min (vagal stimulus). Press the event marker after you have started the paced breathing, and in the end, press the event marker before you stop pacing |
| 5. Supine position | 2 x BP measurement |
| 6. Upright position | standing up at least 5 min, BP measurement 1 x at 3 min (sympathetic stimulus). Press the event marker when the subject starts to get up. |
| 7. Sitting position | Put thee heart rate monitor on. 6 min exercise, bicycle ergometer, HR 90 - 100/min monitored with HR monitor |
| 8. Supine position | 10 min rest, the last 5 min for HRV, measurement of breathing frequency for 1 min between 7 - 8 min |
| 9. Supine position | end of Holter with a 1-min ECG rhythm strip check. Take electrodes and the HR monitor away |

10. Sitting position spirometry

7.12 Procedure identification

Assign each recording (cassette) with a unique identification code of one set of letters and two sets of numbers according the respective SOPs (ULTRA/KTL-F-1.0, ULTRA/UoW-F-1.0). In the beginning, the project name ULTRA 2 and procedure identification code ECG, SPIRO (spirometry) or URI (urinary sample) are stated. After this, a three digit number indicates the study center and subject: 100 - 299 = Amsterdam, 300 - 499 = Erfurt, and 500 - 699 = Helsinki. Finally, a 6-number set indicates the date of the recording (DDMMYY).

The urinary samples are labeled with stickers. E.g. ULTRA2-URI-699-010399 indicates that the urinary sample is collected in Helsinki on March 3, 1999 in a subject number 699.

7.13 Quality control

The quality control requirements of each procedure must be followed carefully. Any deviations from the protocol or any difficulties during the visit should be marked the clinical visit log book.

8. DATA RECORDS

During the visit a clinical visit log book with a questionnaire is filled in, which includes data on time of the start of each procedure in the clinical visit protocol. In addition, data on the ambulatory ECG recording, spirometric lung function measurement, blood pressure, breathing frequency and a 1-minute ECG recording on a paper print in the beginning and at the end of the Holter recording are collected. The data are recorded in ULTRA 2 study subjects. The recorded Holter tapes and copies of clinical visit logbooks will be sent to Kuopio University Hospital for analyses weekly. No X-ray protection is needed for the tapes. The address is

Department of Clinical Physiology / ULTRA
Kuopio University Hospital
P.O.Box 1777
FIN-70211 Kuopio
Finland

Tapes recorded with different recorders should be readily available when opening the package in order to be able to check the tapes easily. The fax number of the Department is + 358 - 17 - 173 244.

9. SAMPLE ARCHIVING

The sample archiving will be conducted in the institutes according the respective information protection rules. The original results of spirometry, ECG paper prints and clinical visit log books are to be archived in the respective institutes. The original Holter tapes will be archived

in KTL. A copy of the data and paper prints of the analyses will be archived in Kuopio University Hospital. The original urinary sample results are archived in the laboratory analyzing the results and copies of them are archived in respective centers.

10. IMPLEMENTATION AND APPLICATION

The SOP for ambulatory ECG recording in ULTRA 2 study (ULTRA/KTL-F-1.0), instructions of the manufacturer of the Holter recorders, the SOP for spirometry in ULTRA 2 study (ULTRA/UoW-F-1.0) and the study protocol manual of ULTRA 2 include also information to implement and apply the present SOP properly.

This SOP will be distributed by KTL ULTRA center to all ULTRA centers by mail or telefax. Reception of a new SOP or revision should always be confirmed to KTL ULTRA center.

11. ATTACHMENTS

Figure 1. Clinical visit log book and questionnaire.

Figure 2. Local and temporal deviation from or local change of SOP ULTRA/KTL-F-2.0.

Figure 3. SOP confirmation sheet.

Figure 1. Clinical visit log book and questionnaire.

CLINICAL VISIT LOG BOOK:

Patient Identification number: _____

Date: _____

Nurse filling out the questionnaire: _____ (number)

Interview: YesDiary changed: YesUrine sample: Yes

No, why? _____

1. ECG 1 min strip: Nurse id: _____

No. of Holter recorder: _____ No. of patient cable: _____

Were there difficulties to locate the electrodes like previously? Yes No

If yes, please specify why:

Start the recorder and set the time of the recorder to 00.00. Start the stopwatch.

Real time of start of Holter recording. _____ h _____ min

Wait 45 sec gain setting period.

Wait 1 min for the calibration signal.

2. Rest in supine position 5 min: Time since start: _____ m _____ sec

Breathing frequency for 1 min, between about 3 - 4 min:

Press the event marker.

_____/min

Press the event marker in the end.

3. Paced breathing for 5 min: Time since start: _____ m _____ sec
(Press the marker after first the paced period)

Press the event marker.

Press the event marker in the end.

4. Blood pressure measurements in supine position:
1. _____/_____ wait 45 sec 2. _____/_____

5. Standing for 5 min: Time since start: _____ m _____ sec

Blood pressure at 3 min: _____/_____

Press the event marker.

Press the event marker in the end.

6. 6 min exercise: Time since start: _____ m _____ sec
HR in the end: _____/min Load in the end: _____ W

Press the event marker.

Press the event marker in the end.

Exercise test complete? Yes No

If no, the exercise test had to be stopped, because

development of symptoms (specify): equipment problems: other (specify):

Questions for the patient:

Did you experience shortness of breath during the exercise test? Yes NoDid you experience chest pain during the exercise? Yes No

7. 10 min rest in supine position: Time since start: _____ m _____ sec

Breathing frequency for 1 min, between about 7 - 8 min:

Press the event marker.

_____/min

Press the event marker in the end.

8. End of Holter: ECG 1 min strip:

9. Spirometry: Number of spirometer: _____ Nurse id: _____

Maneuver complete: Yes No

If no, the maneuver had to be stopped, because:

the patient was unable to perform development of severe symptoms equipment problems other (specify)

Add remarks on the other side

Date: _____ Subject ID: _____

QUESTIONNAIRE

1. Did you have chest pain yesterday? Yes / No
2. Did you have chest pain or other symptoms of angina pectoris during the preceding hour?
If yes, no exercise Yes / No
3. Did you have shortness of breath yesterday? Yes / No
4. Did you have shortness of breath during the preceding hour?
If yes, no exercise Yes / No
5. Did you have wheeze during the preceding hour?
If yes, no exercise Yes / No
6. Did you have an airway infection in the past two weeks? Yes / No

An airway infection is considered to be present if cold, flue, influenza, throat pain, cough, sinus infections or exacerbation of chronic bronchitis are present.

If yes:

6.1 Do you have it today? 7. Did you have fever in the last week? If yes, no exercise

Comment for the nurse: Do you think the subject can perform the exercise?

If no: Why? resp. Infection does not want other (specify)

Yes / No9. Did you visit a doctor for any acute illness during the past 2 weeks? Yes / No

If yes:

For what reason?

Angina Pectoris? Other cardiac? Specify. Respiratory condition? Specify. Urinary tract infection? Other. 10. Did you stay in the hospital because of this illness? Yes / No11. Has there been any changes made in your prescriptions? Yes / NoIf yes, please specify dose and brand name as prescribed. *(update the medication sheet)*

Date: _____ Subject ID: _____

12. Did you take your medication today as prescribed? Yes / No
 If not, please specify:

13. Did you use any inhalator in the last 4 hours? Yes / No

If yes: beta-agonist cortical steroids anti-cholinergic

If question 13 is answered with 'YES', wait with performing the pulmonary function test until one hour has passed.

14. Did you smoke during the past 2 weeks? Yes / No

If yes:

14.1 How many cigarettes in total did you smoke during the past 2 weeks?

1-5 / 6-10 / 20-40 / 40+

14.2 Did you smoke in the last hour? Yes / No

If question 14.2 is answered with 'YES', wait with performing the pulmonary function test until one hour has passed.

15. Have you been in rooms where people smoked during the last 24 hours? Yes / No

15.1 If yes, how long did you stay there? Hours

16. How did you arrive to the clinical visit?

Walking/ cycling car/ bus/ tram metro

17. How many cups of coffee or tea did you drink during the last 4 hours? _____ Coffee cups

17.1 Did you drink coffee during the last hour? _____ Tea cups

17.2 Did you drink tea during the last hour? Yes / No

18. Did you drink alcohol during the last 24 hours? Yes / No

Figure 2. Local and temporal deviation from or local change of SOP ULTRA/KTL-F-2.0.

Identification code:	Center: _____
Deviation Change No:___ pages___	Approval by Principal Investigator
Begin date: __/__/__ End date: __/__/__	Date and Signature: __/__/__ _____
Original text(s); full paragraph, page No:	Changed text(s), full paragraph:

Figure 3.

SOP CONFIRMATION SHEET THE FLOW OF THE CLINICAL VISIT IN ULTRA 2 STUDY

This SOP has been received by Principal Investigator of

Research center _____ Date ___ / ___ / _____

Signature of PI: _____

INSTRUCTIONS :

0) **Keep this sheet attached to the original copy of the corresponding SOP**

1) When copying the SOP, mark the date of copying for each copy, number each copy

2) When delivering the SOP copy, take the signature and mark the date

3) When delivering a new revision to this SOP, collect previous SOP copies away and confirm with signature and mark the date

4) After each change fax this sheet to coordinator

Copy	Date of the copy	Delivered to Signature	Date of delivery	Received back PI signature	Received back Date
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

Coordinator fax : + 358 - 17 – 201 265