Admission criteria to ERSPC

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Participation within the ERSPC clearly will have a number of advantages but will also carry a number of obligations. While this list will mainly indicate the obligations of potential participants upfront, a number of advantages should be mentioned.
Full participation within ERSPC will allow participation in financial assets of the Foundation ERSPC, it will guarantee free participation in all meetings of the Scientific Committee, it will create an opportunity for participation in publications in accordance with the publication policy of the group and it will give the opportunity to contribute in a significant way to a large European scientific endeavour.
Major functions, which are related to the study such as chairmanship of committees, tasks in interim evaluation or coordinatorships of side studies decided by the whole group will be available preferably to those who have an active input into the study by means of producing a randomised sample of participants.

General requirements:

1. A participating centre should be situated, and invite possible participants to the study, within a European country.
2. The centre should have a local study design in agreement with the minimal design requirements, allowing the production of information in line with the minimal data set.
3. The centre could clearly define, to all parties involved, that the study is focussed to establish the effect of screening for prostate cancer and all parallel studies could and should not interfere with this focus.
4. The centre must have conducted a pilot study phase, of which the ERSPC Scientific Committee (SC) accepts the results as being sufficient proof for the quality of future data. The pilot study/studies must have been approved by local ethical committee(s). The pilot study should test and establish effectively all medical and administrative procedures and establish the co-operation necessary to comply with the minimal ERSPC data set.
5. The local ethical committee must give approval of the definitive study protocol.
   In a randomised screening study, identical treatment should be applied to the screening and to the control arm given similar stage and grade. In the case of this study, however, cancers detected within the randomised-screening arm ought to be treated actively since a differentiation of aggressive and non-aggressive cancers is not possible. In this sense within the screening arm, the group has agreed on an intention to treat. [It will be important to compare during the course of the study the distribution of treatment between the participating centers]. Prostate cancer mortality is the major endpoint of the study. Quality of life evaluation is recognised as an essential component.

ERSPC is heterogeneous in many respects that are reflected in differences in national protocols; these differences can only be overcome by mutual agreement. The bodies that may identify and correct such differences are the Data Monitoring Committee (DMC), Scientific Committee (SC) and the Epidemiology Committee (EC) which represent all active participants. Decisions reached within the SC are binding for participants. The DMC is the ethical watchdog of the study. It will establish stopping rules and review the study.

6. It is essential that all participating centers follow the consensus and strict adherence to the decisions of the SC is needed as well as agreement on and adherence to the minimal data set and

the publication policy. Site visits to obtain quality control are to be accepted and reported by the centers.
7. Participating centers agree to provide data to the DMC as necessary for the evaluation of any of the local studies. These data should include the minimum data set applied locally, a description of the procedures of how the data are obtained, a description of the mechanisms of identification of interval cancers and cancers within the control gout as well as contamination by screening tests, migration, and prostate cancer and overall mortality in the study population.
8. All changes in design or protocol have to be approved by the DMC, advised by the epidemiological experts and the SC.

Obviously, during the course of the study it may happen that one of the centers can not comply with the general or specific requirements for participation in ERSPC. In that case, the available data may be reviewed by the DMC (if this Committee is ready to accept this task) or alternatively by the SC which will then have rights to advise exclusion of that local study.
A deadline for including future participating centers will be established, taking into account the number of men enrolled and the quality of initial screening results and organisation of already participating centers.
A final evaluation will be done 10 years after the last patient has been randomised into the Rotterdam protocol; this is anticipated to be in June 2008. The participants will then have had a 10-year follow-up. After that, the evaluation of the major endpoint will be a continuous process. Interim evaluation will be done at least every two years.

Specific requirements in ERSPC:

1. The possible target population has to be randomised to a study arm or a control, arm by individual randomisation. Exceptions to this scheme are subject to approval by the SC and DMC.
2. The minimum number of anticipated screens per centre is 10,000 when considering an individual randomisation.
3. Age of first invitation should be 55 to 70 years. Exceptions require approval.
4. The process of recruitment and repeat screening for men recruited to the intervention arm of the study must be continuous (no interruptions of more than 4 months).
5. The principal test applied within ERSPC is PSA. With additional tests by DRE and TRUS, according to agreed indications. A PSA assay is uniform to all centers. The Hybritech Tandem E or Tandem R assays have been chosen for quality considerations. In case an important technical development during the recruitment time of the study occurs with respect to the improvement of the specificity of the screening procedure with maintenance of the sensitivity, the SC may decide to change the screening procedure. In that case, the regulations of the Hybritech contract under point 6 apply.
6. The biopsy policy is ultrasound guided sextant biopsies and biopsy of possible lesions, if PSA equals 4 or more, or if DRE or TRUS is positive.
7. An adequate proportion of men having biopsy recommended should be biopsied (more than 80%).
8. All criteria also apply for the cycles of re-screening.
9. The rescreening interval is 4 years. Other screening intervals can be considered by the SC. New centers are to be approved as full participants by the SC. Re-investigation of screened men earlier (some form of suspicion left after initial assessment) should be documented.
10. The duration of follow-up is minimally 10 years and preferably longer.

11. The accumulation of follow-up data must be continuous. One simple parameter is the continuous identification of prostate cancers, prostate cancer death and disease non-related deaths in the screening and in the control group.
12. Data accumulated must be in line with the agreements reached concerning the Centralised Database.
13. Data will be critically evaluated as agreed previously by the chairpersons of the Centralised Database, the Quality Control Committee and the Scientific Committee.
14. The Centralised Database will provide data for critical review to the chairman of the Quality Control Committee.
15. It is left to the Quality Control Committee to carry out site visits as necessary for the implementation of these criteria.
16. Failure to live up to Primary Quality requirements is identified by the group and in force by actions of the Quality Control Committee.

Parallel studies

Side studies are permissible within ERSPC; they should not have any influence on the possibility of answering to the main questions regarding the major endpoints (prostate cancer mortality and quality of life) and should not be related to the major endpoints. Side studies should be presented and discussed in the SC and at least approved by its chairman. The agreed publication policy applies.

Minimal dataset for common analysis

1. ALL STUDY SUBJECTS

1.1. BASELINE INFORMATION

REQUIRED

- centre
- ID (study numbers)
- Date of birth
- Date of invitation to participate/informed consent/randomisation
- Arm (screening/control)

OPTIONAL

- race
- socio-economic status, education
- co-morbidity (especially prostatic disease and their treatment whether medical or surgical)
- prostate cancer screening history, contamination

1.2. FOLLOW-UP

REQUIRED

- type of follow-up (active/passive)
- vital status
  - alive
  - dead
  - lost to follow-up (emigrated/no contact)
- date of last contact/record linkage
- date of death
- causes of death
  - autopsy (yes/no)
  - prostate cancer as cause of death should be ascertained by a special committee
  - use of standard code of death certificate is insufficient
  - acquisition of hospital records is encouraged
- Exclusion after randomization
  - Date
  - Reason (refusal/prevalent prostate cancer at randomization)

2. SCREENING ARM ONLY
   REQUIRED
   - date of attendance
     - for each screening round
   - screening test(s) performed
     - results (for each test)
     - further procedures indicated
   - diagnostic test(s) performed
     - date of test(s)
     - type of test (e.g. DRE, TRUS, sextant/directed biopsy)
     - result or reason for failure to perform the test (for each test)
     - severe complication of test (e.g. fever, bleeding following biopsy)
     - final diagnosis or further procedure (e.g.intensive/normal follow-up)

   OPTIONAL
   - date of invitation/reinvitation

3. ALL PROSTATE CANCER CASES IN BOTH ARMS
   (INCLUDED NON-COMPLIERS IF FEASIBLE)
   REQUIRED
   - date of diagnosis
     - method of diagnosis, mode of diagnosis, confirmation
       - Clinical, chemical, radiological, cytological, histological
   - morphology
     - according to the International Classification of Disease for Oncology ICD-O
   - way of detection
     - n screening arm
       - screening/interval/non attendee
     - in control arm
       - symptomatic/opportunistic screening/other
     - incidental cancers diagnosed at autopsy should be excluded in both arms
   - stage at diagnosis
     - according to cTNM and when possible pTNM in the UICC (1992)
   - tumour grade
     - result
     - classification system (Gleason/WHO)

- primary treatment
    - treatment within two months of diagnosis
    - date of (start of) treatment
        - radical prostatectomy
        - residual disease (yes/no)
        - radical radiotherapy
            - excluding palliative radiotherapy
        - hormonal treatment
            - type of treatment
        - transurethral resection
        - watchful waiting
- side-effects and complications of treatment
    - treatment related mortality
    - impotence
    - urinary incontinence
    - cystitis
    - proctitis
- Progression/relapse
    - date of progression/relapse

OPTIONAL

- staging procedures performed
    - results for each: e.g. bone scan, limphadenecytomy (open/laparoscopic)
- other prognostic indices (flow cytometry, immunohistochemistry)
- type of progression/relapse (local, regional, distant, PSA elevation)
- treatment of progression/relapse
- date of active clinical follow-up and outcome

4. INFORMATION ON AGGREGATE LEVEL

- Data on contamination levels (i.e. prevalence of screening test in the control arm) for each screening test at baseline and during the trial at least from a sample of the population)

Criteria for continued participation in ERSPC

The scientific world has become aware of ERSPC as one of the major efforts to clarify the issue of early detection and treatment of prostate cancer, one of the top-health care priorities in the field of cancer. In spite of the decentralised character of the study, conduct in accordance with methodological quality criteria of each centre is essential in order to preserve scientific respect for the total study. Next to the scientific goal, our co-operation is driven by the recognition that not one of the national studies in itself is likely to be able to resolve this issue. We have agreed to co-operate. We have published a common evaluation plan together with our partners in the United States and we have agreed on rules for a central data collection. This co-operation is obligatory and the protection of those centers that live up to previous agreements as well as the protection of the scientific goal requires us to establish "criteria for participation". While the group has agreed on a central data collection and periodic review and a mechanism has been established for the acceptation of centers within ERSPC, the group has never discussed and agreement has never been reached on criteria for continued participation. To establish such criteria is the goal of this document, which should be signed by the co-ordinators of each of the participating centers together with the chairman of the Quality Control Committee, the Epidemiology Committee (Centralised Database) and the Scientific Committee.

Purpose: to assure continued participation first and second grade criteria for continuous participation in ERSPC is established. This is driven by the need to assure the scientific value of the study, to protect valid data from dilution by less valid data and to protect the image of ERSPC to the outside world.

Second grade criteria: ERSPC is based on a sample size calculation, which is critical. Not meeting commitments in this respect may jeopardise the study as a whole. Anticipation and dealing with such problems is necessary in a prospective fashion. Second grade criteria for continued participation are in general discussed within the Scientific Committee and a common solution is found together with the national center that experiences difficulties. The mechanism of placing such issues on the agenda of a Scientific Committee meeting is identical for the outline given for first grade criteria. Second grade criteria are those which do not comprise the value of the data collected by ERSPC for evaluation of its primary end-point.

Second grade criteria are:

1. Failure to meet recruitment promises.
2. Failure to live up to decisions taken by the group as a whole or by the Scientific Committee.
3. Failure to live up to Secondary Quality requirements identified by the group and in force by actions of the Quality Control Committee.
4. Examples for second grade criteria based on Scientific Committee decisions are proper and timely reporting to the central database. Adherence to the publication policy, adherence to the rules for side studies, establishment of causes of death according to group rules, implementation of decisions of the Quality Control Committee, and many others.

While failure to meet first grade criteria will usually be noticed and brought up by the chairman of either the Epidemiology Committee (central database), the Quality Control Committee or the Scientific Committee, criticism in line with definitions of second grade criteria may be brought up by any participant of ERSPC. The international co-ordinator (chairman of the SC) pursues these matters

in an organisational sense. For both, first and second grade criteria, the follow-up procedures will include the production and provision to ERSPC and the international study co-ordinator of a programme of improvement in writing. Prove of implementation of this programme is expected to be given after a six-month period. The Scientific Committee can allot a longer time period if indicated.

Sanctions: Non-compliance with a grade one criteria for participation will usually lead to exclusion of the center from ERSPC in the sense that (some or all) data will not be used in the final evaluation or that their use will be limited to certain aspects of the evaluation. Also, such centers will be taken off the list of participants used in publications. Obviously, such centers can also not participate in stipends given to the group.

Access to and publications related to the central data collection ERSPC.

1. Data collected by the EC data centre are under control of the Scientific Committee with the understanding that:
   a. Data related to the main endpoint of the study remains confidential at the level of the DMC and a small group within the EC: the chairperson of the EC, Prof. Van der Maas and Dr. Ciatto, chairman Qcc, mr. Smith, chairman DMC.
   b. The EC reports to the DMC yearly and to the SC 6 monthly, prior to the group meeting.

2. Publications by the data centre and EC are limited to methodological, issues, side studies or special projects. All such plans for publication must be made with the prior agreement of the Scientific Committee.

3. Data held by the data-centre may be the source of data for side-studies initiated by other groups. In this event:
   - The side study shall be approved by the SC.
   - The protocol for extraction of the data shall be approved by the EC.
   - In each instance the SC shall determine whether:

     a. the data set for analysis shall be exported to those conducting the analysis
     b. the data set shall <u>not</u> be exported but the data cente staff will conduct the analysis following a protocol agreed with those leading the analysis.

4. The "ERSPC Study Group" publishes publications with respect to main endpoints of the study. A writing committee and all participating investigators proposed by the individual centres are co-authors and mentioned in a footnote.
5. Any centre, which withdraws from ERSPC, will have its data removed from the central database and have the data at its disposal.

This policy is agreed and signed by:

The chairpersons of the participating centres and committees:

Place: _____Date:_____

Country/Committee	**Name**	**Signature**
Belgium (Antwerp)		
Finland (Tampere,Helsinki)		
France (Toulouse)		
Italy (Florence)		
The Netherlands (Rotterdam)		
Spain (Getafe)		
Sweden (Göteburg)		
Switzerland (Aarau)		
Epidemiology Committee		
Data monitoring Committee		
Quality Control Committee		