Reviewer's report

Title: Early screening for Chlamydia trachomatis in young women for primary prevention of pelvic inflammatory disease (i-Predict): study protocol for a randomized controlled trial

Version: 0 Date: 29 Jul 2017

Reviewer: Nuria Porta

Reviewer's report:
The i-Share study is first referred in page 9 (design/setting) and comes a bit as a surprise. It is then later described succinctly in page 11. Please move to background to give context to the reader, and add further details (e.g. what is the overall aim of the i-Share cohort study?).

Please add section "Status of trial", including when it was open to recruitment, expected end of recruitment and timing for primary analysis.

The control arm is sometimes referred to as "current guidelines" of screening. This can be a bit misleading, as regular samples are being taken on these patients; despite the analysis of them being deferred, the control arm could not be considered "the current screening guideline". This could be inferred in pg. 14 Primary outcome and from the discussion in page 19. A group following 'current recommendations' would not be taking samples every 6 months; they would undoubtedly be more aware of the issue. Undoubtedly, the challenge with the design is the choice of control group and the ethical challenge of deferring the testing - the team explain the arguments in favour in the discussion, but maybe could elaborate as to whether this was discussed and challenged in the process of set-up and approval of the trial.

Secondary objectives, page 9: 2nd bullet point text between brackets is a bit unclear "at the beginning and end of infection, throughout the course of infection" -- what does this refer to? progression to PID relative to Ct infection start? Not clear.

How is Ct clearance defined? (page 9) This does not appear in Endpoints (page 15).
Page 10, exclusion criteria: the POPI trial excluded patients that had been tested for Chlamidya in the past 3 months, was this considered in this trial? Is pregnancy the only exclusion criteria?

Page 11: Vaginal samples were also self-taken as in the control arm. Please explain consistently the intervention in both arms and highlight the differences.

Trial assessments in pages 10 to 14 could be organised in a sequential order for better flow, i.e. please explain first Recruitment, treatment allocation (with details of randomisation), baseline assessments and follow-up (as in Figure 2), with the following considerations:

- How patients on the iShare cohort study are contacted? I.e. search on patients fulfilling inclusion criteria are contacted directly through the system? Is this what is intended with the description of the information retrieved from the system (e.g. type of training, registration etc. at the top of page 12)? It is unclear if that is used for screening patients or as baseline information for the patients consenting to the trial. I understand the trial also accepts volunteers from i-Share or UHS who would proactively would contact the team to participate in the study.

- The initial visit does not necessarily need to occur after randomisation - would be even better to occur before, after consent and collection of M0 sample and completion of questionnaires.

- Randomisation section: Last sentence (rando after recruitment, obvious) and aim of it unclear. This section needs to explain how the allocation sequence is concealed (I understand the web system generates new codes and access to any pre-specified list is restricted to personnel not directly related to contact with participants). I think the correct term is "block randomisation" or "randomisation by blocks", not "blocked".

- Follow-up: it is unclear how data from clinical episodes will be collected: when Ct is diagnosed in the intervention group, patient is referred to their physician or nearest STI, and the physician upon examination would fill-out a specific form on clinical findings. So, do you contact with (any) physician or STI clinic the patient decides to go? Or she is referred to the trial sites only and they know about trial procedures?

- Same for when patient refers pelvic pain and is contacted to attend a GED, the contact to physician to fill in the information is performed?
Page 14 Outcomes: lines 344-346 could go in background section. If there is controversy around definition of PID, you could say "For the purposes of this trial, PID will be defined as follows".

Page 15 Secondary endpoints:
- Prevalence is listed as 2ary objective but not as 2ary endpoint. Please check objectives and endpoints are aligned.
- Can you clearly define duration of Ct infection, proportion of infections associated with diagnosis of PID (is it Ct diagnosed at PID diagnosed?), time to develop PID (since baseline, Ct infection?), spontaneous Ct infection resolution (e.g. Ct positive at 6 months, but Ct Negative at 12 months? Is that even possible? How do you investigate this, can it be patient taken antibiotics for another reason? Error of Ct diagnostic test?).
- Calculation of re-incidence refers to ref. 21 in page 15, and to refs. 25-26 in page 16: do they refer to the same procedure? If so make it clear or add ref. 21 to page 16; so it's not mistaken by 2 different methods.

Statistical analysis:
- I could not replicate exactly the sample size: could you please provide further details?
- The primary endpoint is cumulative incidence (at 18-24 months/last assessment, binary), and the primary analysis will be on an Intention to Treat basis. How will you consider dropouts without PID diagnose (i.e. pts dropping out before final assessment) - assume no PID?
- If using Cumulative incidence, a Cox model is not adequate (rather it should be logistic regression, as primary endpoint is PID yes/no. Cox model would be adequate to model time to PID.

Section Stakeholders' contributions could go within the text, in a section Trial Governance. Please remove contact details of the monitor of the study, not needed for the manuscript -rather explain the level and extent of monitoring for this trial. Remove "Independent experts" from this section as this has been already explained in the text.

Order of figures do not correspond to legends and reference in text, please amend.
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