Author's response to reviews

Title: Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: Protocol for the SUSPEND trial, a multicentre, placebo controlled, randomised trial of a calcium channel blocker (nifedipine) and an alpha-blocker (tamsulosin)

Authors:

Sam McClinton (s.mcclinton@nhs.net)
Kathryn Starr (k.starr@abdn.ac.uk)
Ruth Thomas (r.e.thomas@abdn.ac.uk)
Graeme McLennan (g.maclennan@abdn.ac.uk)
Gladys McPherson (g.mcpherson@abdn.ac.uk)
Alison McDonald (a.mcdonald@abdn.ac.uk)
Thomas Lam (thomasbllam@abdn.ac.uk)
James N'Dow (j.ndow@abdn.ac.uk)
Mary Kilonzo (m.kilonzo@abdn.ac.uk)
Robert Pickard (r.s.pickard@ncl.ac.uk)
Ken Anson (ken.anson@stgeorges.nhs.uk)
Jennifer Burr (jmb28@st-andrews.ac.uk)

Version: 3 Date: 9 April 2014

Author's response to reviews: see over
Trials
C/o BioMed Central
236 Gray's Inn Road
London
WC1X 8HB

Dear Sirs

RE: 2000245211111787 - Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: a multicentre placebo controlled randomised trial of a calcium channel blocker (nifedipine) and an alpha-blocker (tamsulosin).

We thank the reviewers for their considered comments and provide our response below. A copy of the revised manuscript with changes tracked is attached for your review. As requested we have also included a short discussion of the main operational issues in conducting the trial.

Please do not hesitate to contact us should you have any further comments or queries on our manuscript.

Yours sincerely

Professor Sam McClinton
Response to reviewer Jacques Lacroix.

1. There are two consecutive colons in the title (Use of drug therapy in the management of symptomatic ureteric stones in hospitalized adults: a multicenter placebo controlled randomised trial of a calcium channel blocker (nifedipine) and an alpha-blocker (tamsulosin): study protocol of the randomised controlled SUSPEND trial). As far as I know, this is not optimal English.
   The title has been amended to read:-
   Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: Protocol for the SUSPEND trial, a multicentre, placebo controlled, randomised trial of a calcium channel blocker (nifedipine) and an α-blocker (tamsulosin)

2. A reviewer underlined that the authors mentioned that “Consideration of the frequency of monitoring reports, interim analysis and any criteria for stopping rules will be discussed and agreed with the DMC prior to recruitment starting”. Since the trial started a long time age (January 2011), this sentence must be updated.
   The wording has been amended to the following
   The DMC will meet once 300, 600 and 900 participants have been randomised to discuss interim analysis reports and the criteria for stopping the trial.

3. References, figures and author’s contributions
   Apologies, these have been amended as defined

Response to reviewer Luc Valiquette

Thank you for your expert opinion.

Response to reviewer Josée Bouchard

1. The follow-ups at 4 and 12 weeks are based on postal questionnaires (and chart review), so the response rate may not be excellent. Formal follow-up visits would have been more accurate to assess the primary study objectives. What is the expected percentage of missing response rate based on enrolled participants so far? In addition, what is the percentage of participants seen in clinic at approximately four weeks after randomization?
   The primary outcome of this pragmatic trial is need for further treatment which is first assessed through the participant’s medical records and then validated against the patient reported data. At four weeks 100% of CRFs have been completed and 64% of patient questionnaires have been returned. A study visit would be an unnecessary burden for participants and potentially we would have seen low compliance due to this.

2. In the UK, what is the percentage of patients who seek medical or surgical follow-up outside their primary physician office or initial hospital consultation? Could this affect the results of the study if a significant percentage of follow-up is missing?
   There is very little transfer between hospitals within the UK. Within the trial we ask participants in their 12 week questionnaire whether they have had treatment for their ureteric stone at a hospital other than the one where they were recruited and only 0.5% have reported this to be the case. The authors do not consider this to be a threat to the validity of the trial, but it is an issue we have been aware of and have been monitoring since the trial began.
3. **The spontaneous passage of ureteric stones decrease progressively after 5 mm. Will the authors look at the results based on stones less than 5, 5-7 (or 8) and 8-10 mm and not only less or more than 5 mm?**

The reviewer raises an interesting and valid point. We currently plan to perform sub-analysis for stones ≤ 5mm or >5mm - 10 mm. However the suggested analysis may be included as a post-hoc analysis within our final report.

4. **The authors mentioned that patients on digoxin and rifampin will be excluded from the study. However, this criterion is not listed in the 'official' exclusion criteria.**

The exclusion criteria ‘contraindication to tamsulosin and nifedipine’ includes those medications.

5. **The authors mentioned that ‘Consideration of the frequency of monitoring reports, interim analysis and any criteria for stopping rules will be discussed and agreed with the DMC prior to recruitment starting.’ However, the recruitment has started in January 2011. Additional explanation should be provided on interim analysis.**

This wording has been amended in response to this comment to the following:-

“The DMC will meet once 300, 600 and 900 participants have been randomised to discuss interim analysis reports and the criteria for stopping the trial.”

6. **The authors mentioned on page 5 that nifedipine is contraindicated in pregnancy. However, nifedipine is regularly used for hypertensive disorders in pregnancy (see Seely et al, NEJM 2011: 365:439-46).**

The information regarding nifedipine and pregnancy is taken directly from the Summary of Product Characteristics from the manufacturer of Coracten, the brand of nifedipine used in the trial which states “Because animal studies show embryotoxicity and teratogenicity, nifedipine is contraindicated during pregnancy”.

7. **Finally, what is the role of the funding source?**

The mission of the National Institute for Health Research, funded by the UK government’s Department of Health, is to maintain a health research system in which the NHS supports outstanding individuals, working in world class facilities, conducting leading edge research focused on the needs of patients and the public. The Health Technology Assessment programme fund independent research about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS. The role of the funder is to provide the financial resources to conduct the study. They have oversight of the trial provided in regular update reports provided by the trial office and Trial Steering Committee and Data Monitoring Committee meeting reports (they do not see the confidential DMC report, only the minutes from the open meeting).