PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU).
AUTHORS	Heltveit-Olsen, Silje Rebekka; Sundvall, Pär-Daniel; Gunnarsson, Ronny; Snaebjörnsson Arnljots, Egill; Kowalczyk, Anna; Godycki-Cwirko, Maciek; Platteel, Tamara; Koning, Hilde; Groen, Wim; Åhrén, Christina; Grude, Nils; Verheij, Theo; Hertogh, Cees; Lindbaek, Morten; Hoye, Sigurd

VERSION 1 – REVIEW

REVIEWER	Bakhit, Mina Bond University, Centre for research in Evidence-Based Practice
REVIEW RETURNED	04-Jul-2022

GENERAL COMMENTS	Manuscript title: Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU). Summary Thanks for the opportunity to review this manuscript. It is a well-written, easily digested protocol to assess whether methenamine hippurate can reduce the incidence of UTIs in older women with recurrent UTIs. Minor Revision 1- Few of my patients described that methenamine hippurate pills have a "bitter" or an "awful" taste. It would help if the authors explained how this would be tackled to avoid unblinding of participants. If it was not feasible to mask the taste completely, investigators could check with patients whether they were able to tell if they were in the intervention or placebo arm. 2- Can you please clarify whether the residents of nursing homes (or Residential aged care facilities) are included/excluded from participation in the study? 3- I wonder if the history of a recent hospitalisation or being a Nursing Home resident is one of the confounding variables to be adjusted for in the analyses. Can the authors please clarify? 4- Page 6- Telephone follow-up in case of acute UTI episode(s): can the authors please clarify whether this will be a follow-up with patients directly or the health service provider at each location? 5- If it permits, it will help check the treatment's acceptability on top of measuring compliance. 6- Page 8: Please add the reference/link for the tool used for randomisation (Research Ransomiser)

	7- It will help if the authors used the Template for Intervention Description and Replication (TIDieR) checklist https://doi.org/10.1136/bmj.g1687 with the SPIRIT checklist.

REVIEWER	Roberts, Matthew Royal Brisbane &Women's Hospital, Urology
REVIEW RETURNED	02-Aug-2022

GENERAL COMMENTS	Thank you for asking me to review this paper and well done to the authors on addressing this important clinical topic in such a comprehensive way. My comments are relatively minor and mostly to help improve reader clarity: 1. There is limited reference to the ALTAR trial which currently is the pivotal trial on the topic. I suggest: a) Introduction - please expand on the 1 line reference to the ALTAR trial (and perhaps reduce the emphasis on lower quality retrospective studies) b) Methods - where it is stated that this study is unique etc. please clearly delineate how this study is different to the ALTAR trial (as many clinicians won't know the difference) 2. An important point to mention in the Intro or discussion is the diversity in available clinical guidelines, mostly due to the lack of large high quality studies like this one. This was recently covered in a nice review article doi: 10.1111/bju.15756 3. Please make time references consistent (e.g. six months in one section, 180 days in tables) 4. It seems a bit unclear as to when the study team is notified of when participants have UTIs. It is stated that participants will be followed for 7 days after UTI but how do they know in the first place? Are participants expected to notify them? 5. How will the analysis happen if a clinical service prescribes antibiotic prophylaxis or prolonged course (>7 days) during the course of the trial? This is an exclusion criterion but what if it happens after randomisation? 6. The assumption of 25% reduction in antibiotic prescriptions for the power calculation, what is the basis for this? Retrospective or pilot data? 7. Will the type of antibiotics be considered? E.g. Fosfomycin is a stat dose for 3 day duration, so that could count as 1 treatment compared to amoxicillin which might be 12 treatments/doses over the same duration 8. I would suggest defining "antibiotic treatments" as I assume this means a course, rather than number of tablets (which vary between regimens)

VERSION 1 – AUTHOR RESPONSE

Response to comment by Reviewer 1

Dr. Mina Bakhit, Bond University

Point 2: Thanks for the opportunity to review this manuscript. It is a well-written, easily digested protocol to assess whether methenamine hippurate can reduce the incidence of UTIs in older women with recurrent UTIs.

Response 2: We thank the reviewer for the time, elaborate assessment, and positive feedback. No changes were made in the manuscript in response to this statement.
Point 3: Few of my patients described that methenamine hippurate pills have a "bitter" or an "awful" taste. It would help if the authors explained how this would be tackled to avoid unblinding of participants. If it was not feasible to mask the taste completely, investigators could check with patients whether they were able to tell if they were in the intervention or placebo arm.

Response 3: The placebo tablets will have identical shape and size and markings as the methenamine tablets. The taste of the placebo tablets will not be identical to the methenamine tablets. However, none of the participants has received treatment with methenamine hippurate before, so they will not know what methenamine tablets taste like vs the taste of the placebo. The patients were instructed to swallow the tablets whole. Adding an extra coating/gel capsule was discussed as an option, but we decided that making the study medication even larger could potentially interfere with compliance given the original size of the study medication, study population in question, the twice daily regime and long-term treatment.
We have not had unblinding or patients withdrawing from the study because of the taste of the study medicine so far in this study.

We have added information about shape and size of the placebo tablets in the revised manuscript.
Point 4: Can you please clarify whether the residents of nursing homes (or Residential aged care facilities) are included/excluded from participation in the study?

Response 4: We thank the reviewer for making us aware that this is not explicitly stated in the manuscript. We have not included patients living in nursing homes. Most nursing home residents in the participating countries would not be able to fulfil the strict inclusion/exclusion criteria for a long-term drug study. We have clarified this in the manuscript.

Point 5: I wonder if the history of a recent hospitalisation or being a Nursing Home resident is one of the confounding variables to be adjusted for in the analyses. Can the authors please clarify?

Response 5: We do not include nursing home residents. We ask the participants if they have previously been diagnosed with diabetes, anomalies of the urinary tract, urinary tract stones, pyelonephritis or urosepsis, but we do not collect information about recent hospitalisations. We have clarified this in the manuscript.

Point 6: Page 6- Telephone follow-up in case of acute UTI episode(s): can the authors please clarify whether this will be a follow-up with patients directly or the health service provider at each location?

Response 6: All telephone follow-ups are performed with the patient directly. We have clarified this in the manuscript.

Point 7: If it permits, it will help check the treatment's acceptability on top of measuring compliance.

Response 7: As methemine hippurate in a prophylactic regimen is widely used in the Nordic countries, we did not incorporate treatment’s acceptability in this study. We do see that it could have added to the study, and we will keep it in mind for future studies.

Point 8: Page 8: Please add the reference/link for the tool used for randomisation (Research Randomizer)

Response 8: A reference for the Randomizer has been added to the revised manuscript.

Point 9: It will help if the authors used the Template for Intervention Description and Replication (TIDieR) checklist https://doi.org/10.1136/bmj.g1687 with the SPIRIT checklist.

Response 9: The checklist has been filled out and added to the supplementary files. According to the checklist, we have also included a model patient pocket card in supplementary files.

Response to comment by Reviewer 2
Dr. Matthew Roberts, Royal Brisbane & Women's Hospital

Point 10: Thank you for asking me to review this paper and well done to the authors on addressing this important clinical topic in such a comprehensive way.

Response 10: We thank the reviewer for the time, elaborate assessment, and positive feedback. No changes were made in the manuscript in response to this statement.
Point 11: There is limited reference to the ALTAR trial which currently is the pivotal trial on the topic. I suggest:
a) Introduction - please expand on the 1 line reference to the ALTAR trial (and perhaps reduce the emphasis on lower quality retrospective studies)
b) Methods - where it is stated that this study is unique etc. please clearly delineate how this study is different to the ALTAR trial (as many clinicians won't know the difference)

Response 11: We thank the reviewer for this suggestion. We agree, and have incorporated more information about the ALTAR study and what distinguishes that study from the ImpresU study. The changes are located in the introduction of the revised manuscript.
Point 12: An important point to mention in the Intro or discussion is the diversity in available clinical guidelines, mostly due to the lack of large high quality studies like this one. This was recently covered in a nice review article doi: 10.1111/bju.15756

Response 12: We thank the reviewer for pointing us in the direction of this review article. Clarification of guidelines for prophylactic use of methenamine hippurate is indeed one of our goals with this study, and we have incorporated the topic into the revised manuscript –both in the introduction and the discussion.

Point 13: Please make time references consistent (e.g. six months in one section, 180 days in tables)

Response 13: We thank the reviewer for this input. We agree that one should be consistent throughout a paper. We deliberately chose to use the term six/twelve months in the bulk text for readability. We have deleted the reference to days in the text, but kept it in table 1: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure for the ImpresU clinical trial - as this table refers to specific data collection time points.

Point 14: It seems a bit unclear as to when the study team is notified of when participants have UTIs. It is stated that participants will be followed for 7 days after UTI but how do they know in the first place? Are participants expected to notify them?
How will the analysis happen if a clinical service prescribes antibiotic prophylaxis or prolonged course (>7 days) during the course of the trial? This is an exclusion criterion but what if it happens after randomisation?

Response 14: We thank the reviewer for making us aware that these aspects were not explained in a clear manner in the submitted manuscript.

The patients themselves are instructed (both orally and written) to contact the study team on the designated study phone every time they receive a course of antibiotics/a delayed prescription of antibiotics for a suspected UTI from their GP or other health care services.

If a participant is prescribed prophylactic antibiotics after randomisation, the participant will stop study medication and be asked for permission to continue data collection. If the patient does not want to continue to contribute to data collection (withdraws consent), the patient will be withdrawn from study participation. If the patient wishes to continue to contribute to data collection (discontinue medication, but not withdraw consent), the patient will be followed up with registrations in the same framework as if the patients was receiving study medication for the whole 12 months of the study.

If a patient is prescribed a prolonged course of antibiotics (>7 days,) it will be registered in the UTI episode follow-up forms. We will follow up on the participant every seven days until the UTI episode has resolved. If, during this follow-up, it is decided that the patient will continue urinary antibiotics as long-term prophylaxis, the participant will discontinue study medication as described above.

We have clarified these aspects in the revised manuscript.

Point 15: The assumption of 25% reduction in antibiotic prescriptions for the power calculation, what is the basis for this? Retrospective or pilot data?

Response 15: The assumption of 25% reduction is not based on previous data, but on expert opinion. We concluded in the study team that a reduction of antibiotic prescriptions smaller than 25% was clinically less relevant, so we decided to only look for an effect that is 25% reduction (or larger). We have added this information to the revised manuscript.

Point 16: Will the type of antibiotics be considered? E.g. Fosfomycin is a stat dose for 3 day duration, so that could count as 1 treatment compared to amoxicillin which might be 12 treatments/doses over the same duration.

I would suggest defining "antibiotic treatments" as I assume this means a course, rather than number of tablets (which vary between regimens)

Response 16: We thank the reviewer for this comment, and we agree that it would be wise to define the term “antibiotic treatment” in this manuscript.
We will collect information about type of antibiotics, dosage and duration, but our primary outcome measure is the UTI episode – which we measure by number of antibiotic courses given for suspected UTIs.
We have defined the term “antibiotic treatment” in the revised manuscript to clarify this in accordance with the reviewer’s suggestion.

We will collect information about the duration of the treatment to be able to calculate number of UTI episodes in accordance with our definition of a UTI episode (14 asymptomatic days since the last day of antibiotic treatment for the previous UTI episode).

VERSION 2 – REVIEW

REVIEWER	Bakhit, Mina Bond University, Centre for research in Evidence-Based Practice
REVIEW RETURNED	17-Sep-2022

GENERAL COMMENTS	I would like to thank the authors for their responses to my comments and queries. I have no further comments or revisions.